VOLUME 27 NUMBER 1

JAN 20 1921

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Archives of Internal Medicine

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A STUDY OF UNUSUAL ENDOCRINE DISTURBANCES; THEIR ASSOCIATED MYOPATHIES, ENDOCRINE BALANCE AND METABOLISM FINDINGS

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NEW YORK SAN FRANCISCO

In a series of cases studied at the U. S. Army General Hospital No. 41, Fox Hills, Staten Island, N. Y., over a period of five months, such interesting manifestations were noted from an endocrinologic and myopathic standpoint, that their publication seems warranted.

REPORT OF CASES

CASE 1.—*An advanced instance of polyglandular disturbance, characterized by a dystrophia adiposo-genitalis, precipitated by influenza, associated with a muscular dystrophy, and unusual reactions of the vegetative nervous system. A consideration of the endocrine balance and the metabolism findings is of unusual interest.*

C. G., white, aged 27 years, was a motorman and rancher by prewar occupation. Habits: Alcoholic beverages indulged in moderately. Used tobacco. He smoked about a dozen cigarettes daily; a pipe occasionally.

Family History.—Father living and well; mother dead of unknown cause; no brothers or sisters. No history of tuberculosis; no nervous, mental or endocrinologic diseases in the family.

Previous History.—Pneumonia and measles in childhood. Mumps in February, 1918, unassociated with any testicular involvement. No venereal diseases.

Present Illness.—This dates its inception to an attack of influenza in July, 1918. At that time he was in bed one week, and suffered from pains in his bones, malaise and weakness. He states that his temperature reached 106 F. on a number of days, and he then was delirious.

In the latter part of July, 1918, he was returned to duty, stayed at the front about ten days and then was sent back to the hospital for a right-sided pleurisy, which had appeared during his initial attack of influenza. He remained in the hospital this time for seven weeks, suffering from a fibrinous pleurisy (right side). In October, 1918, he again returned to duty, remaining in that status until March, 1919.

During this period (October, 1918, to March, 1919) he noted the beginning of his present illness. Pain in the right chest appeared; weakness of the lower extremities even to the extent of falling, and sleepiness became manifest. At the same time, he noticed that his testicles were getting smaller and softer; that his skin and hair were getting dry and brittle, that his hips were broadening with peculiar deposits of fat, and that his breasts were getting larger, especially the right.

In March, 1919, he again entered the hospital where he remained until about May 1. These symptoms progressed, and, in addition, he noted a frequency of urination. In the beginning of the illness he lost about twenty pounds of

weight; then there followed an increase in weight which has continued ever since, until now he weighs 240 pounds.

In July, 1919, he was sent back to the United States. About this time, in addition to the definite progression of the other symptoms noted, a craving for sweets and a loss of erections, libido and ejaculatory reflex became evident; although prior to this time he was quite virile, there have since been but few erections or feelings of sexual desire. A change of voice (its pitch becoming raised) began at this time.

He has also noticed that his upper extremities have grown in length. An increased thirst has developed in the past few weeks.

Gastro-Intestinal: His appetite is rather capricious. Bowels: Normal. Vomiting: Of considerable frequency in the past six months. It is unassociated with abdominal pain or hematemesis. A "sour stomach" with gaseous

Fig. 1 (Case 1).—Dystrophia adiposogenitalis.

and acid eructations accompanies this symptom, together with a sense of fulness in the abdomen. There is no relation to the intake of food; the vomiting is aggravated by the acid eructations and alleviated by an empty stomach.

Genito-Urinary: No dysuria or hematuria. The sexual deficiencies have been mentioned. No history of enuresis.

Respiratory: No cough; no hemoptysis. Sharp and stabbing pain occurs in the right lower chest, at times. No history of epistaxis.

Cardiovascular: A considerable degree of shortness of breath is present. There is edema of the legs when he is up and about. Dizziness and a tendency toward syncope are likewise noted.

Central Nervous System: Headache is an insignificant symptom seldom complained of, and when present, is vertical in type. No complaints in the spheres of vision or hearing. A certain amount of emotional instability is complained of, manifested by his getting upset more easily than heretofore.

Skin: Shaving was begun at the age of 17 and resorted to once or twice a week until about a year ago. Since that time, the period between shav-

ings has increased considerably, until now it is hardly necessary. Many attacks of urticaria have occurred in the last few years.

Neurologic and General Physical Examination.—NEUROLOGIC: 1. Cranial nerves negative: Pupils equal, react fairly well to light and accommodation; they are fairly round in contour. The fundi and the fields of vision display no abnormality; no hemianopsia.

3. Reflexes: Knee jerks, right much diminished, left absent. Achilles tendon jerk, left much diminished, right absent. No Babinski, Oppenheim or no past-pointing.

2. Cerebellar functions: No adiadokokinesia; no manual or pedal ataxia; Chaddock phenomena; no ankle clonus. The middle and lower abdominal reflexes are present. The cremasteric reflexes are not always elicited; when they are, a diminution is noted.

4. Motor: Motor power is well preserved in the upper extremities. The muscles of the thigh, viz., quadriceps extensors, hamstrings, abductors and the glutei are considerably weakened, especially the abductors, the hamstrings, and the flexors of the thigh (pelvofemoral) are involved, whereas the inverters, evertors, flexors and extensors of the feet are fairly powerful. This stands in direct contrast to the fact that the legs are much thinner than the thighs (pseudohypertrophy of thighs?).

Fig. 2 (Case 1).—The genitalia.

Electrical Examination.—Examination was confined to three muscles on the left side, the tibialis anticus, gastrocnemius and quadriceps extensor. Faradic response was obtained in all three muscles; but it was weak and appeared only when the primary coil was completely covered. A quick galvanic response, without tetanus or reversal, was obtained from all three muscles; but the reaction did not start to appear until the current reached 15 milliamperes.

Examination with the Jones' condensor: A barely perceptible response was obtained with the following strength in microfarads, using 100 volts: Tibialis anticus, 0.02; gastrocnemius, 0.08; quadriceps extensor, 0.07.

In the control, a normal person, a response was obtained with 0.01 microfarad in all three muscles.

SUMMARY: Marked diminution of faradic and galvanic irritability. The reaction of degeneration is not present. A waddling gait is present, associated with lumbar lordosis.

Sensory: The appreciation of all forms of sensation seems slightly diminished on the left side, with the exception of the muscles and joint sense which seems to be well preserved on both sides. The sensory findings vary, and areas of anesthesia (touch) are found on the dorsum of the feet; pain appreciation,

heat and cold perception, however, are well preserved. Vibration sense is lost in both lower extremities. The sensory abnormalities disclosed are inconstant, and are definitely of a functional nature. Reexamination at intervals of months reveals no essential change in the sensory sphere.

6. Psychiatric examination reveals no abnormalities. The patient is neither depressed nor taciturn.

General Physical Examination.—The figure is of a feminine type. Deposits of fat are especially noted over the iliac regions and the buttocks, in the pubic region and on the lower abdomen. A collar of fat in the neck obscures the thyroid cartilages (pomum Adami); a questionable enlargement of the thyroid gland is present. Special deposits were noted on the outer aspects of both thighs and in the breasts. The breasts are notably large, the right being larger than the left (Fig. 1).

The skin is quite smooth, soft, pinkish and dry; its thinness, as determined by the hypodermic needle, deserves special mention. The skin is quite easily bruised. The face is beardless; the hair is dry and stiff. The configuration of the genital hairs is distinctly of a feminine type (Fig. 1) the hair in this region and in the axilla being quite sparse.

The testicles are quite small and atrophic; the scrotal folds surround the penis, like labia, being inserted laterally to the penis (Fig. 2).

Fig. 3 (Case 1).—The teeth.

The teeth are small; abnormal spacing is noted between the incisors; especially the lower central incisors. The upper central incisors are rather large. The canines simulate the incisors, and lack the fang form (Fig. 3).

The hands are large, but not unusually so.

With the exception of the bilateral genu recurvatum and genu valgum, and the marked lumbar lordosis, hyperextensibility is not found in any other joints.

Nose and Throat: Aside from deflection of the nasal septum to the right, no other nasal abnormalities found. The tonsils are moderately large; the pharynx is negative.

Ears: The ears reveal normal hearing, and are normal to labyrinthine (Bárány) tests.

Eyes: The pupils are usually dilated and react well to light and accommodation; on convergence, the left eye quite constantly fails (i. e., swings outward). Vision: Oct. 14, 1919, right, 20/30 plus; left, 20/30 plus; 1 degree esophoria. Ocular movements good in all directions. Fields show no defects in either eye. Outside of very slight blurring in the left disk margins, both fundi are negative. Conclusions: No ocular abnormalities noted. Feb. 9, 1920, vision was, right, 20/20; left, 20/20. No change since above examination. March 1 and March 20, 1920, perimetric examination to form and color was normal. June 5: Fundi and perimetric examination to form and color were normal.

Lungs: Normal.

Heart: The point of maximum intensity is not seen. The left border is 0.5 cm. outside the left nipple line; at the apex the first sound is heard rather weakly; a soft systolic murmur is heard at the apex, but it is not transmitted The action of tryamin reveals a normal cardiac response.

Blood Pressure: Taken at intervals of two minutes.

Pulse	Blood Pressure	
	Systolic	Diastolic
90	122	80
90	122	82
90	120	85
94	120	84
90	122	85
90	122	84
94	122	84

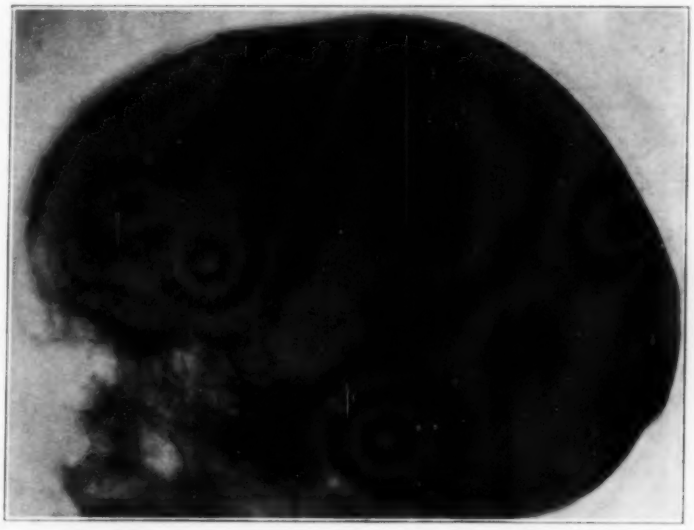

Fig. 4 (Case 1).—Roentgenogram of the sella turcica.

When taken at intervals of one minute, the blood pressure was:

Systolic	Diastolic
122	85
122	85
122	84

Aside from a slight increase in the pulse rate, no other abnormalities are found.

Cyanosis is not noted in hands or feet. Edema of a moderate degree is found in the lower extremities, more especially after exertion.

Abdomen: No viscera are palpable. The markedly adipose pendulous abdominal wall has been mentioned; numerous striae are seen here as well as over the thigh. Rectal examination reveals an unusually small, firm prostate.

Glands: No special adenopathy.

Temperature: Records taken daily, every hour or two, for three weeks show a range between 98 F. in the morning and 99.4 F. in the afternoon. The afternoon and evening rise are quite constant.

LABORATORY DATA

	Feb. 9, 1920	Feb. 22, 1920	May, 1920
Erythrocytes	4,100,000	5,400,000	
Leukocytes	8,200	9,200	7,600
Hemoglobin, per cent	85	90	80
Differential Count:			
Small mononuclears, per cent	14	20	16
Large mononuclears, per cent	10	3	12
Polymorphonuclears, per cent	76	77	72

BLOOD CHEMISTRY *

Blood sugar (fasting stomach, March, 1920), 0.058 per cent.

Blood sugar curve (May, 1920)

	Blood Per Cent.	Urine
Fasting	0.078	None
One hour after taking 183.5 gm. glucose	0.140	None
Two hours afterward	0.104	None

Blood sugar curve (August, 1920): Determined four months later when the patient was gaining weight rapidly, having attained 250 pounds.

	Per Cent.
Fasting	0.133
One half hour after taking 183.5 gm. of glucose	0.238
Two hours afterward	0.312
Three hours afterward	0.232

(* These determinations were made in the laboratory of Dr. George Draper.)
Urea nitrogen: 15.4 mg. per 100 c.c. of blood (May, 1920).
Blood creatinin: 1.97 mg. per 100 c.c. of blood (March, 1920).
Blood creatinin: 1.4 mg. per 100 c.c. of blood (May, 1920).
Blood creatin: 4.1 mg. per 100 c.c. of blood (May, 1920).
Blood uric acids: 2.3 mg. per 100 c.c. of blood (May, 1920).
Blood calcium: 11.7 mg. per 100 c.c. of blood (April, 1920).
Blood carbon dioxid: 62.4 volume per cent.
Blood Wassermann reaction was negative Oct. 17, 1919, and Feb. 10, 1920.
Bleeding time: 2 minutes.
Coagulation time: 4½ minutes.

FECES

March 1, 1920: Mucus, negative; muscle fibers, few striated and nonstriated fibers present; fat, moderate; starch, negative.

March 3, 1920: After the ingestion of 200 gm. fat in the form of butter, the color was dark brown; consistence, hard; mucus, negative; blood, free (occult), negative; muscle fiber, none; fat, moderate amount; no appreciable increase of this substance over that found on previous examination; starch, negative.

STOMACH CONTENTS

Oct. 21, 1919	March 5, 1920
Free hydrochloric acid, negative	27
Occult blood, negative	Negative
Total acidity	59

SPINAL FLUID

Pressure, normal; transparency, clear; cell count two; globulin, negative; Wassermann, negative; colloidal gold curve, normal for preliminary and final curves.

URINE

Numerous urine examinations were made at varying intervals. They all revealed:

Amber color; clear; acid; specific gravity varying between 1.010 and 1.030, with an average of about 1.022; albumin, negative; sugar negative; acetone, negative. Casts were not found at any time. The average output of eight twenty-four-hour observations was 1,300 c.c. with a range of from 750 to 1,900 c.c. Phenolphthalein showed 25 per cent. output for the first hour; 40 per cent. for the second hour; total, 65 per cent. Total nitrogen, 11.7 gm.; uric acid, 0.47 gm.; urinary creatin, 0.09 gm.; urinary creatinin, 1.4 gm.

Sugar Tolerance Test (Alimentary Glycosuria).—No glycosuria after 100 gm. glucose, after 183 gm. glucose, after 100 gm. glucose with 1 c.c. of 1: 1,000 epinephrin solution, hypodermically, nor after 150 gm. glucose with 1 c.c. of 1: 1,000 epinephrin, hypodermically.

Pathology.—A specimen of muscle removed from the biceps of the right thigh showed on gross examination a distinct pallor. Histologic examination "does not appear to show any pathologic change of importance. There is some fatty infiltration, but the muscle bundles themselves do not exhibit any evidence of degeneration or other lesion of significance." (Dr. K. M. Vogel.) These findings indicate very strongly the early stages of muscle dystrophy.

Roentgen-Ray Findings

Chest.—Aug. 12, 1919: Apices clear. Moderate amount of peribronchial infiltration on both sides, especially right base.

Heart.—Oct. 5, 1919: Transverse diameter of the heart shadow measures 14 cm. and does not show a definite enlargement, except in the regions of the auricles, and is the type of heart shadow noted in mitral insufficiency.

Head.—October 5: There is noted a deep sella turcica with rather long anterior clinoid process. No other irregularity or deformity noted in the bones of skull. (Fig. 4.)

February, 1920: Lateral stereo of head shows no evidence of pathology about sella turcica. The mastoids are clearly shown and are negative, as to bone pathology. Anteroposterior and lateral views show large frontal sinuses which are clear. Ethmoids and antra are clear. There is a shadow which appears to be a spur on right side of septum.

June 24, 1920: No further change in sella turcica is noted.

Bones.—March 2, 1920: The epiphyses of the lower end of tibia have united, but the epiphyseal line is still evident. This is seen in 90 per cent. of individuals of his age. All other joints taken are negative. A good portion of the shafts of the bones are shown, and also are negative.

Stomach.—March 2: Fluoroscopic examination shows the stomach normal in size and position. Peristalsis active and stomach begins emptying very quickly. Pylorus in midline; no filling defect noted in stomach. The duodenal bulb appears normal. Plate examination confirms fluoroscopic. There is no six-hour retention. The bowel has begun emptying in twenty-four hours and there is still some barium in large intestine in forty-eight hours. No abnormality is noted in the large intestine. Roentgen-ray findings are negative except for a hyperperistalsis in the stomach. Pineal shadow suggestive; thymus shadow absent.

MEASUREMENTS OF PATIENT

	Cm.
Total length	176.5
Circumference of head	57.5
Circumference of chest (at level of nipples)	101
Circumference of abdomen (at umbilicus)	112.5
Sternoclavicular junction to anterior superior spine of ilium	39
Anterior superior spine to internal malleolus	93
Anterior superior spine to upper border of patella	48
Acromion to styloid process of radius	62.5
Acromion to tip of olecranon	34
Distance between acromion processes	42
Distance between iliac spines	25
Spanwidth	192
Penis	5.5
Testes	2.5 × 1
Thigh, right	63
Thigh, left	63
Calf, right	35
Calf, left	35.5
Arm, right	34
Arm, left	32.5
Torso-leg ratio	39/93 or 0.42

EPINEPHRIN TEST (GOETSCH'S)

	Pulse	Blood Pressure—Systolic	Blood Pressure—Diastolic	Symptoms and Signs
Before administration	96	122	90	
Epinephrin, 0.5 c.c., 1: 1,000 solution, hypodermically:				
7 min. later	104	136	88	Patient complains of nervousness. Has moderate tremor of hands.
10 min. later	104	140	84	Tremor and throbbing of vessels and palpitation of heart marked. Patient feels nervous and "shaky."
16 min. later	108	140	88	Tremor, palpitation and nervousness marked.
24 min. later	108	142	88	Marked tremor, etc.
30 min. later	102	145	100	Symptoms as above.
35 min. later	104	150	95	Marked palpitation, tremor, nervousness, pallor. Respiration 22.
60 min. later	112	165	90	Marked tremor, palpitation, throbbing of vessels. First sound at apex sharp with loud systolic murmur.
1 hr. and 30 min. later	110	145	88	Tremor, palpitation, throbbing and nervousness marked.
2 hr. and 10 min. later	120	135	88	Palpitation and throbbing of vessels still fairly marked. Patient still complains of nervousness.

EPINEPHRIN TEST

	Pulse	Blood Pressure—Systolic	Blood Pressure—Diastolic	Respiration	Symptoms and Signs
Before administration	82	112	90	24	
Epinephrin, 1 c.c., 1: 1,000 solution, hypodermically:					
10 min. after	100	148	85	29	"Feels nervous," the outstretched hands show considerable tremor; the face is somewhat blanched. Cardiac palpitation.
20 min. later	100	140	80	35	Tremor marked; considerable cardiac palpitation, with pulsation of neck vessels. Definite pallor.

EPINEPHRIN TEST AND OBSERVATION OF SERGENT'S WHITE LINE (WHITE ADRENAL LINE)

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Symptoms and Signs
Before administration	80	120	80	
Epinephrin, 1 c.c., 1:1,000 solution, hypodermically:				
5 min. later	104	140	80	Tremor fairly marked. Heart thumping, palpitation marked, patient moderately pale, respiration rapid; patient complains of feeling very nervous. *Disappearance of white adrenal line.*
10 min. later	112	140	80	*White adrenal line gradually reappearing, and becoming more marked.* Marked tremor, palpitation of heart, nervousness continuing.
15 min. later	112	145	80	*White adrenal line well marked, notwithstanding a maintenance of the heightened blood pressure.* Tremor, etc., still marked.
25 min. later	115	140	80	*White adrenal line still marked. Blood pressure still high.*
30 min. later	112	135	78	White adrenal line still marked; blood pressure falling; tremor, palpitation, nervousness, still present.

The interest in the above observations attaches to the rapid disappearance of the pure white adrenal line, as described by Sergent, following the administration of epinephrin, and to its rapid reappearance in the face of the sustained increased blood pressure.

The length of time during which the blood pressure (systolic) remained elevated is quite unusual, as is also the persistence of the nervous and cardiac phenomena.

From the above observation it would seem that the presence of the white line depends on factors other than lowered blood pressure.

TYRAMIN AND OBSERVATIONS ON WHITE ADRENAL LINE

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Symptoms and Signs
Tyramin, 60 mg., hypodermically	..	...	..	White adrenal line present.
5 min. later	80	140	78	White line just as marked as before drug's administration.
10 min. later	80	145	80	Intensity of white line same.
15 min. later	64	130	80	Intensity of white line just as marked.

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Respiration	Symptoms and Signs
Before administration of 80 mg. tyramin, hypodermically	100	130	90	40	White line present
5 min. later	64	180	105	70	White line unchanged
10 min. later	68	186	104	78	White line unchanged
20 min. later	80	170	100	62	Temperature, 98.4 F.; white line unchanged

This again demonstrates the persistency of a marked line in the presence of an increased blood pressure, brought about by tyramin.

PITUITARY EXTRACT AND OBSERVATIONS ON WHITE ADRENAL LINE

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Symptoms and Signs
Pituitary extract, 1 c.c., hypodermically, at 11 a. m.				White adrenal line well marked.
5 min. later	..	...	..	White line has disappeared.
10 min. later	..	...	..	White line still not visible.
15 min. later	..	...	..	White line still not visible.
20 min. later	80	110	75	White line barely visible.
25 min. later	..	...	..	White line has appeared again faintly.
				Patient complains of cramps in abdomen, and desire to defecate. Defecation occurred.
Pituitary extract, 1 c.c., hypodermically, at 2 p. m.				
1 min. later	..	...	..	White line present (xx).
2 min. later	..	...	..	White line present.
5 min. later	..	...	..	White line has disappeared.
10 min. later	84	110	70	White line has disappeared.
15 min. later	..	...	..	White line beginning to appear. (Desire to defecate.) Patient complaining of cramps in abdomen.
20 min. later	..	...	..	White line faint.

PITUITRIN TEST

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Symptoms and Signs
Before administration pituitary extract 1 c.c.	84	120	90	
5 min. later	100 Small volume	120	90	Patient pale. Feels sleepy. Desire to defecate and urinate present. Cramps in abdomen.
10 min. later	96 Small volume	120	90	
15 min. later	96 Small volume	120	90	Movement of bowels occurred.

ATROPIN TEST

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Respiration	Symptoms and Signs
Before administration.....	80-84	122-126	80	16	
After administration 1/75 gr., hypodermically, given at 9:15 p. m.					
9:25 p. m.....	68	112	70	22	Pupils dilating; dryness of mucous membrane beginning.
9:45 p. m.....	80	116	90	44	Considerable dryness of mouth, tongue and pharynx; pupils dilating further; feels hot; face flushed.
10:15 p. m.....	90	135	100	48	Marked dryness complained of, producing distress. Pupils widely dilated. Respiratory rate increasing further.
10:30 p. m.....	88	135	100	45	Same as 10:15 p. m.
10:45 p. m.....	96	135	90	90	Respiratory rate notably increased. Face flushed; skin and mucous membrane quite dry.
11:00 p. m.....	82	135	85	70	Mucous membrane of mouth not quite so dry; pupils still widely dilated.
11:15 p. m.....	80	135	90	38	Respiration less rapid; mucous membrane of mouth and pharynx not so dry. Face less flushed.

PILOCARPIN TEST (1)

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Respiration	Symptoms and Signs
Before administration	100	120	90	28	Skin dry.
Administration of 0.008 gm., hypodermically:					
15 min. later.....	100	134	98	30	Moderate salivation; skin dry. A desire to defecate is present.
30 min. later.....	110	134	98	40	Moderate salivation; skin moderately moist.
45 min. later.....	110	130	95	50	Quite marked salivation and moisture of skin; axilla quite moist; temp. 98.6 F.
1 hour later.....	118	135	100	48	Salivation less marked. Skin less moist; desire to urinate present.

PILOCARPIN TEST (2)

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Symptoms and Signs
Before administration	90	120	85	
Pilocarpin, 0.0065 gm., hypodermically:				
5 min. later	90	120	85	
10 min. later	96	120	80	Moderate salivation; slight sweating.
20 min. later	100	124	80	Quite marked salivation; moderate sweating, slight flushing of cheeks.
30 min. later	..	...	..	White line of Sergent well marked.
30 min. later	100	124	80	Rather marked salivation, skin moist. Patient urinated three times during action of the drug. Patient expectorated about three ounces of saliva.

ERGOTIN TEST

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Symptoms and Signs
Before administration	84	124	80	
Ergotin, 1/10 gr., hypodermically:				
5 min. later	88	122	80	
15 min. later	88	122	80	No special signs or symptoms noted.

PHYSOSTIGMIN (ESERIN) TEST

	Pulse	Respiration	Symptoms and Signs
Before administration	92	34	
Physostigmin, 1/50 grain:			
15 min. later	96	36	Outside of slight headache and slight salivation, no gastro-intestinal effects were noted during the hour following the giving of this drug. Blood pressure readings showed no change.

ASCHNER'S PHENOMENON (OCULOCARDIAC REFLEX)

Pulse, 72: Slight increase to 84. Winking reflex, 13 per minute. Loewi's phenomenon (epinephrin instillation in conjunctival sac). Negative.

GOETSCH'S SKIN TEST

This test was markedly positive. A large central area of blanching surrounded by a peripheral zone of reddening lasted from four to five hours. In the blanched area there was the characteristic goose flesh formation.

In view of the surprisingly high respiratory rates gotten in response to the injection of some of the foregoing drugs, it was decided to determine how much of a psychic factor entered into this peculiarity. Accordingly, 1 c.c. of sterile water was injected subcutaneously. Soon after the respiratory rate rose from 24 to 46. In view of this, the high respiratory rates recorded in the foregoing observations must be discounted considerably.

CUSHING'S THERMO-REACTION

An attempt was made to determine the effect of pituitary extract injections on the temperature; injections were made on six successive occasions. A rise to 99.8 and 99.2 F. occurred on two occasions; the other four injections produced no reaction.

TABLE 1.—SYMPATHICOTONIA

	Case 1	Case 2	Case 3
1. Mydriasis	Positive	Positive	Negative
2. Paralysis of accommodation	Negative	?	Negative
3. Dryness of eyeball	Negative	Negative	Negative
4. Infrequency of winking	Negative	Positive (slight)	Positive
5. Dryness of mouth	Negative	Negative	Negative
6. Low gastric acidity	Negative	Negative	Negative
7. Increased gastric secretion	Positive	Negative	Negative
8. Lessened intestinal tonus	Negative	Negative	Positive ?
9. Constipation	Negative	Negative	Negative
10. Faulty convergence of eyes	Positive	Positive	Negative
11. Wide eyeslits	Positive	Negative	Negative
12. Exophthalmos	Negative	Negative	Negative
13. Tachycardia	Positive (slight)	Positive (slight)	Negative
14. High blood pressure	Slight	Positive (slight)	Negative
15. Vasoconstriction	Positive	Negative (slight)	Negative
16. Relaxation of detrusor of bladder (incontinence)	Negative	Negative	Negative
17. Urticaria	Positive (history)	Negative	Negative
18. Atony of stomach	Negative	Positive	Positive
19. Gastroptosis	Negative	Positive	Negative
20. No dermatographia	Positive	Slight	Negative
21. Tonsils small and atrophied	Negative	Positive	Negative
22. Gag reflex marked	Positive	Negative	Negative
23. Eosinopenia	Positive	Positive	Positive
24. Tachypnea with dyspnea not affected by atropin, i. e., rate not lowered by atropin	Positive	Negative	Negative
25. Dry hands and feet	Positive	Negative	Negative
26. Ashner's phenomenon (oculocardiac reflex) produces no change in pulse	Positive	Negative	Negative
27. Steatorrhea	Negative	Negative	Negative
28. Lowered carbohydrate tolerance before and after epinephrin administration	Negative	Negative	Negative
29. Pilocarpin causes no salivation	Negative	Positive	Negative
30. Loewi's test positive	Negative	.....	Negative
31. Reaction to epinephrin	Positive (marked)	Negative	Negative
32. Pituitary extract	Fairly marked peripheral constriction; movement of bowels	.....	Same
33. Reaction to ergotin	Slight	.....	Slight
34. Tyramin	Marked reaction	.....	Slight reaction

BASAL METABOLISM

1. *March 27, 1920.*—Calories per sq. meter per hour, 29.3. Variation, minus 26. per cent.[1]

2. *April 15, 1920.*—Calories per sq. meter per hour, 35.6. Variation minus 10 per cent. *Antuitrin* (extract of anterior lobe of hypophysis, Parke, Davis & Co.) 1 c.c. was now given hypodermically; 15 minutes after the basal metabolism revealed: Calories per sq. meter per hour, 36.6. Variation, minus 7 per cent.; 45 minutes after: Calories per sq. meter per hour, 34.5. Variation, minus 13 per cent.

The patient was suffering from a rather severe rhinitis and pharyngitis, the temperature ranging from 99.5 to 100, while these determinations of April 15, 1920, were being obtained.

3. *May 6, 1920.*—Basal metabolism determinations with patient on 1 c.c. of antuitrin (Parke, Davis & Co.) by hypodermic, three times daily, for a period of two weeks, together with capsules of orchic extract, 5 grains, three times daily, revealed: Calories per sq. meter per hour, 33.7. Variation, minus 14.5 per cent.

1. Determination made by Dr. B. Sanger, department of metabolism, Presbyterian Hospital. The determinations of April 15 and May 6 were made by Dr. H. E. Marks, department of metabolism, College of Physicians and Surgeons (Columbia University).

COMMENT

Owing to the patient's irregular respiratory excursion, the basal metabolism findings were obtained with difficulty. Such variations, as may be ascribed to respiratory irregularity probably do not amount to more than 4 or 6 per cent. In general, it may be said, that the basal metabolism is lowered, that a decrease is from minus 10 to minus 26 per cent. Administration of antuitrin hypodermically caused little, if any, change, other than the slight rise from minus 10 to minus 7 per cent., either when given *directly* before the basal metabolism determination, or when administered steadily with orchic extract for weeks prior to the determination. In other words, neither a single dose nor the cumulative effects of many doses of antuitrin seemed to alter the basal metabolism.[1]

It seems not unlikely that the nasopharyngeal infection present during the second series of metabolism determinations produced a slight rise. Interpreted in the light of the polyglandular disurbance, the lowering of the basal metabolism indicates that the hypopituitarism present is of much greater intensity than the hyperthyroidism.

PROGRESS NOTES

During the period of observation (six months) certain important additional facts were noted: (1) a marked susceptibility to infection; (2) the gradual development of a slight weakness of the shoulder group of muscles; (3) periods of somnolence; (4) a continuance of gain in weight until 250 pounds were attained in August, 1920; (5) an indolent reaction of the tissues in healing, with relation to the wound in the thigh, through which a specimen of muscle was obtained.

TREATMENT

After a week of thyroid tablets, 0.065 gm., three times a day, dizziness, tachycardia (120), tremor and weakness appeared.

At another hospital, the patient was given whole gland hypophysis (Armour and Co.) over a period of three months. No improvement was noted. In fact, the patient thought he became worse, i. e., his weakness increased. No reduction of weight occurred during this time.

Various combinations of gland products were given in a variety of ways with no real improvement. Extract of whole pituitary gland (Armour and Co.) from 0.33 to 0.66 gm., three times a day, by mouth, with ampoules of antuitrin (Parke, Davis and Co.), 1 c.c., two, and then three, times a day, subcutaneously, together with orchic extract (Armour and Co.), 1 gm. a day

1. It is interesting to note that some very recent investigators[2] likewise noted no effect on basal metabolism from powdered anterior lobe hypophysis by mouth or extract of posterior lobe hypophysis and pars intermedia subcutaneously in a group of similar cases.

2. Snell, A. M.; Ford, F., and Rowntree, L. G.: Studies in Basal Metabolism, J. A. M. A. **75**:515 (Aug. 21) 1920.

by mouth, were given over a period of months without beneficial effect. Owing to the patient's sensitiveness to epinephrin and pituitary extract (posterior lobe hypophysis), the hypodermic administration of these drugs in doses as low as 0.18 c.c. each, three times a day, had to be discontinued.

The vomiting was well controlled by extract of belladonna, 1.2 c.c. five times a day, combined with bismuth subcarbonate, 0.66 gm. and sodium bicarbonate, 1.2 gm., four times a day.

Tincture of digitalis, in the usual dosages, was quite effective in relieving the edema of the legs.

DISCUSSION

1. *The Endocrine Balance.*—While there is no doubt that the picture presented is one of dystrophia adiposogenitalis, it is difficult to differentiate between the hypophysial and pure or primary genital forms of this disorder. Although there is very little evidence on which to involve the hypophysis, namely, no roentgen-ray changes in the sella turcia, no signs of intracranial pressure, no polyuria, no subnormal temperature, and no blood changes (such as eosinophilia, lymphocytosis, low hemoglobin, as noted by Falta [3]), yet, the lowering of the basal metabolism possibly favors pituitary participation as against the pure gonadal or eunuchoid type.[4] The persistently open epiphyses of eunuchoidism are not found here, but as the onset of this affection occurred after epiphysial closure (i. e. after puberty), this differential point is of no avail.

It has been suggested [5] that two other gland disturbances may possibly produce this syndrome, namely, (1) an involvement of the suprarenal cortex; (2) the activity of ovarian rests.

Concerning the former, it may be said that a deficiency of the suprarenal cortex may well affect the genital status and the growth of the body and hair, but we have been unable to find sufficient evidence to postulate such involvement; the same is true of ovarian rests.

Of no little interest is the participation of the other ductless glands in this syndrome. Hyperthyroidism is evidenced by the increased tone of the vegetative nervous system, by the questionable enlargement of the gland, the epinephrin sensitiveness (the pronounced Goetsch test), the increased temperature and pulse rate, and, of most importance, the response to thyroid gland feeding (see Chart 1, Fig. 15). Of especial significance is the increased temperature, for uncomplicated hypopituitarism is accompanied by a *hypothermia.*

As for the gonadal participation, pronounced atrophy of the gonads is quite evident.

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3. Falta, W.: The Ductless Glandular Diseases, Ed. 2, Philadelphia, P. Blakiston's Son & Co., 1916.

4. Falta states "many more investigations are necessary" in reference to this differential point.

5. Timme, W.: Personal communication.

For involvement of the pineal gland, we have the suggestive roentgen-ray shadow and the muscular dystrophy.[6]

Since we regard the white line of Sergent as being a very doubtful sign of hypoadrenia,[7] and with no other certain evidence of deficient suprarenal secretion, the participation of this gland seems very doubtful.

Claude and Gougerot [8] have considered a somewhat allied clinical syndrome some years ago under the caption of "Insuffisance pluriglandulaire endocrinienne," in which an instance of thyro-suprarenal-testicular deficiency was described.

Von Dziembowski [9] reports a case of dystrophia adiposogenitalis with muscular dystrophy in a young man of the same age with findings very similar to those here presented.

2. *Muscle Dystrophy.*—The relationship of the muscular dystrophies to endocrine disturbance was emphasized of late by W. Timme [6] and by Janney, Goodhart and Isaacson.[10] These authors have reviewed the literature on this subject. Timme emphasizes the rôle of the pineal gland; Janney and his co-workers note a polyglandular involvement in which the thyroid, hypophysis, gonads, pineal and supra-adrenals participate.

The latter workers have also drawn attention to the creatin—creatinin and sugar metabolism. In their series of dystrophy case, they found a marked decrease in the urinary preformed creatinin, the abnormal presence of creatin in the urine, low blood creatinin values with a normal amount of creatin in the blood, a hypoglycemia and a delay in the utilization of sugar.

In the case recorded above, there was a normal blood creatin, and the abnormal presence of creatin in the urine. The creatinin in the blood and urine is in normal amounts. This may be due to the limited extent of the dystrophy present in this case at the present time, with the preservation of a good deal of normal muscle function especially in the upper extremities. There is definite hypoglycemia,[11] and a delayed utilization curve present.[12]

In this connection the cardiac weakness manifested by this patient since the onset of the illness may be due to a cardiac involvement in

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6. Timme, W.: Progressive Muscular Atrophy as an Endocrine Disease, Arch. Int. Med. **19**:79 (Jan.) 1917.

7. Kay, W. E., and Brock, S.: The White Adrenal Line (Sergent): Its Clinical Significance, Am. J. M. Sc., to be published.

8. Claude, H., and Gougerot, H.: Insuffisance pluriglandulaire endocrinienne, J. de physiol. et path. gen., June, 1908.

9. Von Dziembowski, S.: Dystrophia Adiposo-genitalis mit Myopathie, Deutsch. med. Wchnschr. **43**:654, 1917.

10. Janney, N. W.; Goodhart, S. P., and Isaacson, V. I.: The Endocrine Origin of Muscular Dystrophy, Arch. Int. Med. **21**:188 (Feb.) 1918.

11. See blood sugar determination of March and May, 1920.

12. See blood sugar determination of August, 1920.

the dystrophic process, a point recently emphasized by Goodhart and Globus.[13]

3. *The Vegetative Nervous System.*—The reactions on the part of the vegetative nervous system indicate a marked hyperirritability, which is predominantly sympathicotonic as evidenced by the pronounced sensitiveness to epinephrin and to the other tests indicative of sympathetic dominance (Tables 1 and 2).

The significant disappearance of the white adrenal line (Sergent) following the administration of epinephrin, with its rapid reappearance deserves mention, the more so as the reappearance of the line occurred while the other manifestations of epinephrin action were still in marked evidence (tremor, cardiovascular symptoms and elevated blood pressure). This fact, as well as other investigations which are now being made on the white line, lead us to hesitate in accepting the alleged dependence of this phenomenon upon a state of hypo-adrenia.

4. *Complicating Infections.*—A noteworthy feature of the case is the patient's susceptibility and reaction to infection. While under observation he has had numerous nasopharyngeal and respiratory infections. In an attack of follicular tonsillitis the pulse rose to 160, respirations to 50, and the temperature to 105 F., remaining thus for forty-eight hours; periods of delirium accompanied the infection. *This indicates a distinct lack of immunity bodies.* The response to infection also reveals certain sympathicotonic characteristics in the symptomatology.

At this point the relationship of influenza to the production of this dysglandular disturbance may be considered. We believe that this individual had always been of the hypopituitary type, that the predisposition to a glandular dyscrasia was latent, and that the severe infection merely served to upset the balance to such a degree as to bring about the marked changes described.

CASE 2.—*A polyglandular syndrome on a definitely hereditary basis, in which a hyperfunctioning of the thymus and suprarenal glands counterbalances a hypopituitary state. Of especial interest are the physical manifestations, the increased muscular power, the roentgen-ray and laboratory findings. Attention is directed to the remarkable contrast offered between this case and Case 1.*

M. C., white, 20 years of age; prewar occupation, laborer. Habits: Negative for alcoholic excesses and drug addiction.

Family History.—Father, paternal grandmother and aunt are very stout, short in stature and possess a convergent strabismus similar to that shown by the patient. The father suffers from "asthma and rheumatism." Mother is small and thin; she has been operated on for gallbladder disease. Brothers:

13. Goodhart, S. P., and Globus, J. H.: On the Nature of Muscular Dystrophies, with a Report of Changes in Cardiac Muscle in Two Cases, Neurol. Bull. **1**:386, 1918.

none. Sisters: one, living and well; she resembles the mother but not the father nor the patient.

Personal History.—He has had measles and influenza; the latter disease kept him in bed about two weeks. No gunshot wounds or other casualties. No venereal infection.

Present History.—The patient was sent to the hospital for mental observation, because of numerous escapades, and infractions of military regulations.

Gastro-Intestinal: Appetite voracious; does not care for candy or sweets. Vomiting, none. No gaseous or acid eructations. Bowels: Four or five movements a day.

Fig. 5 (Case 2).—Dystrophia adiposogenitalis.

Respiratory: No cough; no hemoptysis; no pain in the chest. Epistaxis, seldom.

Nervous System: Headache at times, located in forehead above the eyes; a dull pain getting better as the day progresses, inconstantly present, and sometimes absent for weeks. No especial nervousness; no dizziness; no fainting; no convulsive seizures.

Cardiovascular: Somewhat short winded, getting out of breath on running; no swelling of the feet; no palpitation of heart; no precordial pain.

Genito-Urinary System: Urinates about six times per day. No nocturia; no dysuria; no hematuria; no enuresis. Libido is apparently much diminished; states he entertains no feeling of sexual desire; nocturnal emissions absent. No history of coitus or homosexual practices.

Physical Examination.—The patient is of a short, stout build (Fig. 5), weighing about 180 pounds. The fat distribution is of an adiposogenitalis nature being noted especially in the breasts, lower abdomen, pubic regions and over the iliae. The skin over the abdomen and face is fine, smooth and silky. The breasts show a marked areolae formation.

Hair: The pubic hairs reveal a horizontal upper border simulating the female type. The hair is sparse over the abdomen, face and axillae; the hair on the face is limited to the chin and upper lip, being of the lanugo variety. The hair of the head and eyebrows is rather profuse; that over the lower back, buttock and thighs is considerable in amount, fine in texture and rather sharply delimited from the hairless parts above. Shaving is resorted to twice a week.

A definite degree of pigmentation is noted, especially about the waist and in the axillae.

The patient perspires very profusely.

Fig. 6 (Case 2).—The teeth.

Teeth: The teeth are definitely abnormal. In the upper row, the two central incisors are large; the left lateral incisor is erupted behind the left upper canine. The right upper canine is quite small and resembles an incisor. The lower incisors are irregularly erupted and stunted in growth. The first molars have a fang-like contour. Many cavities of small and large size and some pyorrhea alveolaris are present (Fig. 6).

Genitalia: Testicles are of medium size, situated near the external inguinal ring. The penis is normal in size and in power of erection.

Heart: The left border percusses out one inch beyond the nipple line; rate slow (80 per minute); rhythm regular. A soft systolic murmur is heard over the aortic area; it is not transmitted.

Blood Vessels: Negative.

Thyroid: Not enlarged.

Lungs: Slight dulness right base. No other abnormalities.

Abdomen: Negative.

Glandular and Osseous System: Negative.

Neurologic Examination.—1. Cranial Nerves: Eyes: Right affected with a convergent squint. Pupils: equal, round, regular in contour and reacting to direct and consensual light stimulation. There is some restriction of the field of vision of the right eye incident to the strabismus. No cranial nerve palsy.

2. Motor: *An unusual degree of muscle strength is exhibited by this individual.* He is able to lift and carry very heavy objects, seemingly out of

proportion to his height and general stature. (This capacity has influenced his choice of occupation. He has always worked at very laborious tasks as freight handling, etc.) No tremor is present.

3. Sensory: No abnormalities.
4. Reflexes: Normal; no abnormal reflexes.
5. Equilibration: Normal. No ataxia. No adiadokokinesis.

Psychiatric Examination.—This reveals a definite degree of mental deficiency, with the emotivity, suggestibility, and irresponsibility of a child.

Roentgen-Ray Examination

Chest.—Anteroposterior stereoroentgenogram (Fig. 7) shows a marked retraction in the right lateral aspect where there is a considerable thickening of the pleura; the costophrenic angles are clear. The upper mediastinum

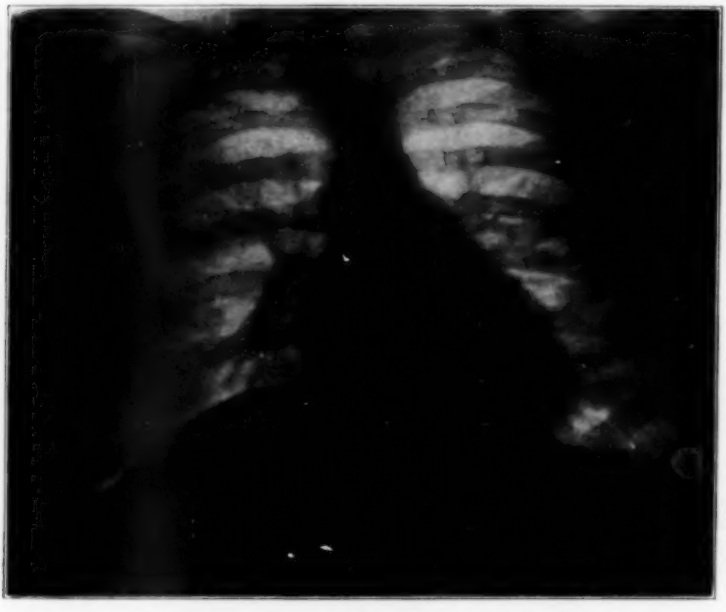

Fig. 7 (Case 2).—Roentgenogram of the chest.

reveals a distinct thymus shadow. The right lung shows considerable clouding of apex. The bronchial trunks reveal considerable thickening. The left lung is negative. The apex does not give the impression of activity. The heart shadow appears moderately enlarged to the left.

Hands.—Anteroposterior view reveals the tapering form to the fingers and the small tufts characteristic of hypopituitarism (Fig. 8). The stereoroentgenogram of wrist joint, including carpus and metacarpus, shows that the epiphysis of the lower ends of the radius and ulna are not united firmly. There is an area of rarefaction at the proximal end of the second metacarpal bone on both sides. The femora and knee joints are negative.

Head.—The lateral stereoroentgenogram reveals a sella turcica which is quite shallow; anterior clinoid processes, which are shortened and blunted,

and a posterior wall seemingly eroded; the posterior clinoid processes are shortened and indistinct (Fig. 9).

Gastro-Intestinal Tract.—Fluoroscopic examination shows a slightly dilated stomach with lower border on level of crest of ilium. Stomach was hypotonic but began emptying in ten minutes. Emptied in midline. Examination of duodenum negative. The two and one-half and six hour plates each shows retention in the stomach. The six hour plate showed that the barium had passed entirely through the small intestines and was then present in the large bowel and rectum. The appendix was visualized in the twenty-four and forty-eight hour plates. The large intestines appear to be entirely empty in forty-eight hours.

Fig. 8 (Case 2).—Roentgenogram of the fingers of hypopituitarism.

The roentgen-ray findings in this case show that patient has a hypotonic stomach; hypertonic small intestines; a residual appendix. The large intestines empty in the normal time.

PHARMACOLOGIC TESTS (VEGETATIVE NERVOUS SYSTEM)

Pituitary Extract	Pulse	Blood Pressure	Symptoms
Before administration ...	85	120-65	
Pituitrin, 1 c.c., hypodermically:			
15 min. later.....	84	125-85	Patient pale; no white line; slight red line.
25 min. later.....	84	120-80	Patient pale; no other symptoms; slight red line. Temp. 98.8 F.
40 min. later.....	80	127-80	Patient still slightly pale; no other symptoms; slight red line.

ATROPIN TEST

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Symptoms and Signs
Before administration	80	122	55	
Atropin sulphate, 1/50 grain, hypodermically:				
10 min. later	80	120	70	Moderate dryness of mouth; pupils dilated; white line present, of moderate intensity.
20 min. later	90	115	65	Patient complains of dryness of mouth; no other symptoms; no flushing; extreme dryness; respiration, 35.
30 min. later	84	118	65	Mouth moderately dry; white line of moderate intensity; no especial symptoms or signs; oculocardiac reflex (Aschner's phenomenon) negative, i. e., no change in pulse; 90 to 86; pupils dilated.
1 hour later	80	122	60	Moderate dryness of mouth; slight dryness of skin; respiration, 26.
Before administration	85	135	60	
Atropin, 1/100 grain:				
5 min. later	90	128	75	No symptoms.
7 min. later	90	130	70	No symptoms.
17 min. later	86	134	70	White line present, of moderate intensity on light pressure; red line on moderately deep pressure; no symptoms.
30 min. later	84	130	80	Slight dryness; white line present, of moderate intensity; red line of moderate intensity intermixed with white line on deeper pressure.
40 min. later	88	130	70	Slight dryness.

PILOCARPIN TEST

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Symptoms and Signs
Before administration	88	138	40	White line present.
Pilocarpin, 1/10 grain, hypodermically.				
10 min. later	88	138	40	Patient feels warm; salivation and perspiration moderate in degree.
25 min. later	88	138	40	Face flushed; moderate perspiration and salivation; marked red line not hitherto noted; white line present on light pressure, but diminished in intensity.
35 min. later	94	134	36	Slight salivation and perspiration; red line not nearly as marked; a mixture of red and white is obtained; white line of moderate intensity.

EPINEPHRIN TEST

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Symptoms and Signs
Before administration (10 min.)	88	130	55	
Before administration (3 min.)	86	132	60	
Epinephrin, 1 c.c., 1: 1,000 solution, hypodermically.				
8 min. later	80	136	45	No especial symptoms.
20 min. later	82	138	45	Moderate palpitation of heart and throbbing of vessels; white line present; no especial subjective signs.
25 min. later	88	134	60	Quite marked palpitation and throbbing of vessels; no tremor; no subjective symptoms.
35 min. later	80	137	30	Palpitation and throbbing less marked; white line much diminished (hardly present); patient has "goose flesh" formation.
50 min. later	80	136	35	Still moderate throbbing of vessels; white line almost disappeared; red line present (no "goose flesh"); patient makes no complaint of symptoms.

MEASUREMENTS OF PATIENT

	Cm.
Total length	160.5
Circumference of head	53
Circumference of chest (at level of nipples)	99
Circumference of abdomen (at umbilicus)	99
Sternoclavicular junction to anterior superior spine	42
Anterior superior spine to internal malleolus	84
Anterior superior spine to upper border of patella	39.5
Acromion to styloid process of radius	49
Acromion to tip of olecranon	30.5
Distance between acromion processes	38
Distance between iliac spines	25
Span width	164.5
Penis (length)	9.5
Testes, approximately	4 × 2.5
Thigh, left	54.5
Thigh, right	54.5
Calf, left	33
Calf, right	33
Arm, left	29
Arm, right	29.5
Torso-leg ratio	½ or .5

Laboratory Data

BLOOD

	April, 1920	May, 1920
Erythrocytes	3,968,000	4,980,000
Hemoglobin, per cent	85	90
Leukocytes	10,200	9,700
Polymorphonuclears, per cent	72	72
Small mononuclears, per cent	22	16
Large mononuclears, per cent	4	12
Transitionals, per cent	2	..

Wassermann negative.

BLOOD SUGAR CURVE

	Blood Per cent.	Urine
Fasting	0.100	None
One hour after taking 132 gm. of glucose	0.108	None
Two hours after taking 132 gm. of glucose	0.121	Very faint trace

CARBON DIOXID TENSION

65.5 volumes per cent.

GASTRIC CONTENTS

Total acidity	70
Combined acids	6
Free hydrochloric acid	34
Combined hydrochloric acid	30
Lactic acid	Neg.

FECES

Color	Brown
Consistency	Soft
Mucus	None
Occult blood	Trace
Fat	Large amount
Starch	None
Muscle fibers	Few

SUGAR TOLERANCE

Glucose, 200 and 250 gm., on fasting stomach, produces no glycosuria in the four hourly specimens taken following its administration.

URINE

The urine is of an amber color; turbid; acid; specific gravity about 1.030; negative for albumin and sugar, and on microscopic examination.

BASAL METABOLISM

Seventy-one and eight-tenths calories per hour; 40.3 calories per square meter per hour. Variation: plus 2 per cent. Essentially normal basal metabolism.

TABLE 2.—VAGOTONIA

	Case 1	Case 2	Case 3
1. Myosis	Negative	Negative	Moderate
2. Epiphora	Slight	Negative	Negative
3. Hyperhidrosis	Negative	Negative	Negative
4. Frequency of winking	Negative	Negative	Negative
5. Salivation	Negative	Negative	Negative
6. Gastric hyperacidity	Positive	Positive	Negative
7. Arrest of gastric secretion	Negative	Negative	Negative
8. Vomiting	Positive	Negative	Negative
9. Diarrhea (8 to 10 times)	Negative	Positive	Negative
10. Gastric hypertonia	Positive	Negative	Negative
11. Spastic colon	Negative	Negative	Negative
12. Enophthalmos	Negative	Positive	Positive
13. Bradycardia	Negative	Negative	Positive
14. Low blood pressure	Negative	Negative	Positive
15. Asthmatic seizures	Negative	Negative	Negative
16. Esophagism	Negative	Negative	Negative
17. Mucous colitis	Negative	Negative	Negative
18. Dermatographia	Negative	Positive	Positive
19. Status thymicolymphaticus	Negative	Negative	Negative
20. Absent gag reflex	Negative	Positive	Positive
21. Eosinophilia	Negative	Negative	Negative
22. Pulsus irregularis respiratorius which disappears with atropin	Negative	Positive	Positive
23. Clammy hands and feet	Negative	Negative	Negative
24. Priapism	Negative	Negative	Negative
25. Oculocardiac reflex	Negative	Positive	Positive
26. Increased fat tolerance	Positive	Positive ?	Positive
27. Increased carbohydrate tolerance before and after epinephrin	Positive	Positive	Positive
28. Salivation induced by pilocarpin	Positive	Negative	Positive
29. Reaction to atropin	Positive	Negative	Negative

DISCUSSION

1. *Endocrine Balance.—Suprarenal*: Hyperfunction of this gland is evidenced by the peculiar hairiness of the individual, slightly increased blood pressure, the increased muscular strength and possibly by the cardiac hypertrophy. The pigmentation noted might well be interpreted as having been deposited during a phase of hypoadrenia, either before the establishment of the present balance, or during upsets incident to infections.

Thymus: The definite thymus shadow indicates participation of this gland.

Pituitary: The peculiar adiposity, the shallow sella turcia, the increased sugar tolerance (evidenced especially in the alimentary tests) bespeak a definite hypopituitarism.

2. *Muscle Function.*—An increased muscle strength is noted, which, as has been mentioned, is out of proportion to his height and stature In Case 1, which stands in peculiar contrast to this case, a muscular dystrophy was noted. While this case occurs in an individual in whom a distinct hereditary tendency may be traced, the first patient has no ascertainable hereditary basis.

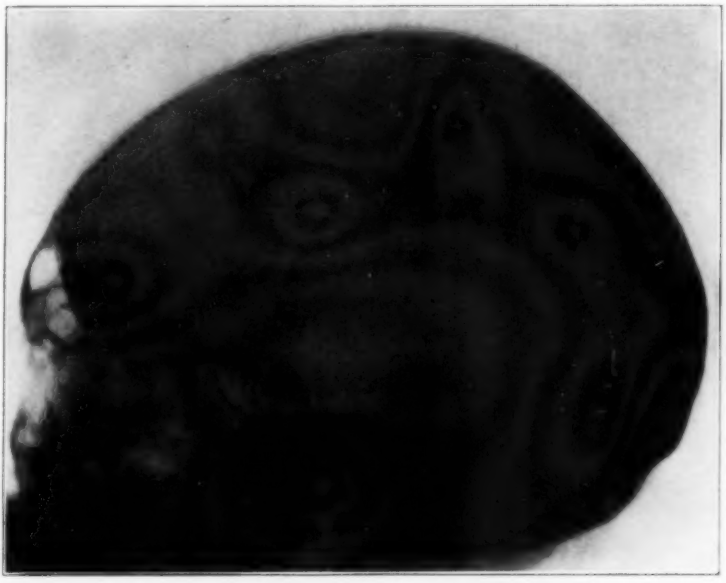

Fig. 9 (Case 2).—Roentgenogram of the sella turcica.

It is difficult, if not impossible, in the present state of our knowledge, to explain satisfactorily the increased muscle strength of the one and the dystrophy of the other—to apportion to this or that gland even its relative importance, or to ascribe to any one gland, definite relationships to muscle function.

This uncertainty is enhanced not only by the multiplicity of glands playing a part, but also by the fact that complicated, subtle compensatory mechanisms are at work tending to establish a balance—attempting a restoration of normal function.

Fig. 10 (Case 3).—The relaxation difficulty in myotonia congenita. The facial expression is indicative of concentrated effort.

It is beside the purpose of this report to enter into the highly theoretical possibilities deduceable.

3. *Basal Metabolism.*—That a balance is struck in this disturbance of the endocrine system is again demonstrated by the essentially normal basal metabolism determination.

4. *Psyche.*—The mental deficiency and inadequate personality reactions present are dependent not on the endocrine dyscrasia but rather on a basic developmental and hereditary defect which involves the psyche on the one hand, and the glands of internal secretion and physical make-up (namely, congenital squint) on the other.

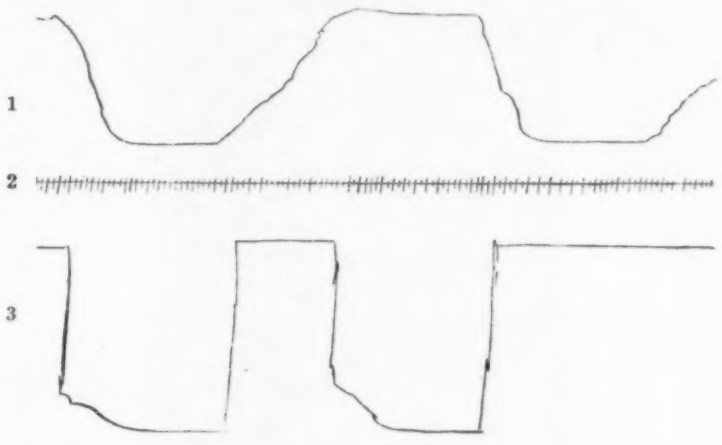

Fig. 11.—The normal and myotonic myogram. 1. The curve in myotonia congenita (Case 3). 2. The time markings in one-tenth second. 3. The normal curve. The downstroke represents contraction; the upstroke relaxation. The same amount of electrical stimulation was used in the myotonic as in the normal control.

CASE 3.—*An instance of myotonia congenita associated with definite endocrine disturbances. A polyglandular syndrome involving a thyroparathyroid gonad deficiency on a probable hereditary basis is described.*

R. L., aged 23 years, laborer. Habits: Tobacco and alcohol used in moderation. Drugs: None.

Family History.—Father living; suffering from cataract; mother living and well. Sisters: three, living and well. No history of epileptic seizures, psychiatric disorders, or any other diseases obtainable. No history of any muscular disorders.

Previous History.—Measles, scarlet fever and varicella in childhood. No venereal diseases.

Present Illness.—Ever since the age of 7 the patient has been subject to seizures, in which a tremor "comes on him." He then falls unconscious (?). He has never hurt himself in falling nor has he bitten his tongue, lip or cheek.

No involuntary passage of urine or feces has occurred. The seizures are of variable duration. On recovery he does not know his whereabouts and is confused. No feeling of fatigue or headache follow the seizures. They are infrequent in occurrence, sometimes being years apart.

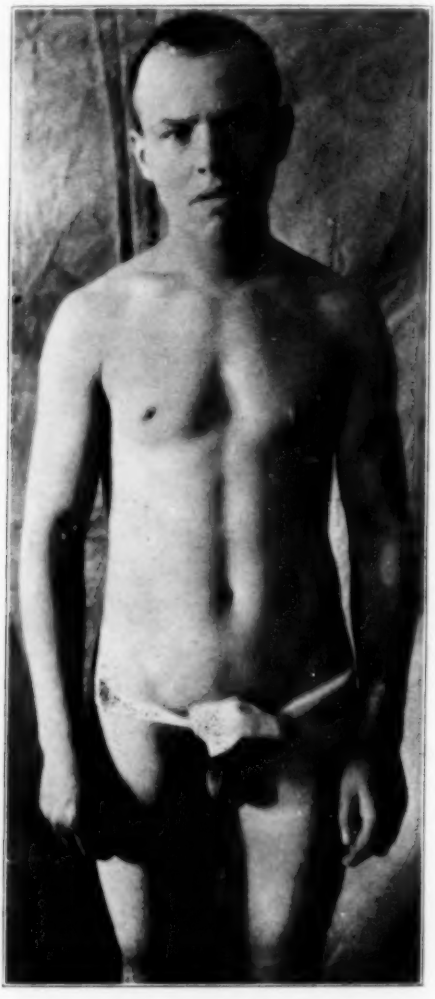

Fig. 12 (Case 3).—Dystrophia adiposogenitalis.

Ever since he can remember he has noted a peculiar difficulty in relaxing the grip muscles of his hands after grasping an object.

Gastro-Intestinal: Appetite good; no craving for sweets. Bowels: Two movements a day. No vomiting; slight gaseous eructations; no pyrosis.

Genito-Urinary: No dysuria or hematuria. No nocturia; no enuresis. Libido: definitely diminished as long as he can remember; he has never had sexual intercourse. No nocturnal emissions.

Respiratory: No cough, no epistaxis.

Cardiovascular: No shortness of breath, precordial pain, or distress. No easy fatigability; no edema of the legs.

Central Nervous System: No headache unless emotionally upset.

Skin: Shaves about two or three times a week although beard is ill-developed. Urticaria: None.

Neurologic and General Physical Examination.—No abnormalities in sensory, reflex or cranial nerve sphere.

Motor: A remarkable myotonia of the so-called myotonia congenita type (Thomsen's disease) is present; especially the grip muscles of the hand are involved making the relaxation of the grip a slow, difficult movement (Fig 10). This preponderating power of the flexors produces a position of the hand very similar to the accoucheur's hand of tetany, especially in the performance of fine movements (such as buttoning the shirt). The mechanical irritability of the muscles of the entire body is quite elevated, remarkable depressions being noted when muscles are mechanically stimulated; the muscle response on mechanical stimulation reveals a sustained plateau of contraction followed by a slow relaxation. This myotonic response is well marked in the tongue, and at times individual facial muscles may be made to undergo slow contraction.

Fig. 13 (Case 3).—The teeth.

In the lower extremities the myotonia produces some slight stiffness in the performance of quick movements, such as rapid squatting movements. While fibrillary twitchings are noted after mechanical stimulation, they are not nearly as marked as the myotonic depression. A greater degree of myotonia was noticed when the patient concentrated all his attention on his muscular efforts.

No Trousseau or true Chvostek phenomenon obtained.

Electrical Examination.—Faradic examination: As compared with controls, a stronger current was required to contract the muscles of the upper limbs. The reaction is definitely slower than normal, and is associated with a persistence of the contraction after removal of the current (myotonic reaction, Fig. 11).

Galvanic Examination: Normal quick response; K C C greater than A C C.

Cerebellar Functions: Normal.

Psychiatric Examination reveals a definite mental deficiency, associated with a very labile emotional state. The suggestibility and lack of inhibition characteristic of the child are in marked evidence. Inability to remain in one place or concentrate on a given task is also characteristic. No other psychic abnormalities.

General Physical Examination.—The facies of the patient is that of a cretin, with a wide nasal bridge, thick lips, a mouth that is habitually open,

a large tongue which is slightly bifid. The eyes have a mongolian slant, and are somewhat deep-set with narrow apertures. A low forehead, quadrangular head and large mouth are noted (Fig. 12). The thyroid gland is definitely enlarged (isthmus and lateral lobes).

The hair of the head is dry and has a markedly convex curve at the forehead margin. The hair on the thighs and in the axillae is moderate in amount, but sparse on the trunk.

The skin and subcutaneous tissue are quite thick, as is very evident on attempts to draw blood or give a hypodermic injection. Dryness of the skin is also a feature.

While the penis is of normal size, the testes are distinctly undersized. The simulation of the labia minora by the scrotal folds is lacking. The pubic hairs are profuse and of a male type.

Fig. 14 (Case 3).—Roentgenogram of sella turcica.

Examination of the teeth reveals upper central incisors which are very large in size; the lower incisors are normal. The lower and upper incisors do not approximate when the jaws are closed, the upper jaw protruding slightly. An elliptical area exists between the upper and lower incisors when the jaws are closed, in addition to the prognathism of the upper jaw. The canines are not fang-like and resemble the incisors. A marked pyorrhea alveolaris is present (Fig. 13). A high palatal arch is noted.

No hyperextensibility of the joints is present.

No adiposogenitalis type of fat distribution.

The terminal phalanges are definitely thickened, the nails are somewhat incurved.

Nose and Throat Examination: Except for a small spur on the left side of the septum, and a hypertrophied right inferior turbinate, the nose is normal. The tonsils are slightly enlarged.

Hearing is normal in both ears. The labyrinthine reactions (Bárány) are normal although sluggish.

Eyes: Vision: right, 20/40; left, 20/40. Ocular movements good; right pupil larger, both pupils active to light and accommodation. Esophoria, 3 degrees. Right hyperphoria, 1 degree. Under homatropin: right, 20/70 — 100, axis 180 degrees; equals 20/50; left, 20/50 — 50, with plus 100, axis 90 degrees; equals 20/50. Both fundi negative. Perimetric examinations to form and color is normal. A compound myopia is present.

Lungs: Normal.

Heart: Normal.

Blood Pressure Observations: taken at 2 minute intervals:

Systolic	Diastolic
100	66
97	66
99	66
100	68
100	68

The pulse has been notably slow ranging in rate from 48 to 84, usually being in the sixties; a marked respiratory (sinus) arrhythmia is present. There is no edema or cyanosis.

Abdomen: No viscera palpable. Rectal examination reveals prostate flat, small, moderately firm.

Glands: No special adenopathy noted.

Temperature Observations: A definite subnormal temperature, ranging between 97 F. in the morning and 98 F. in the afternoon has been observed daily for weeks.

MEASUREMENTS OF PATIENT

	Cm.
Total length	165
Circumference of head	55
Circumference of chest (at level of nipples)	87.5
Circumference of abdomen (at umbilicus)	77
Sterno-clavicular junction to anterior superior spine	39
Anterior superior spine to internal malleolus	82
Anterior superior spine to upper border of patella	41.5
Acromion to styloid process of radius	51.5
Acromion to tip of olecranon	29.5
Distance between acromion processes	36
Distance between iliac spines	24.5
Span width	168
Penis	12
Testes	2 × 1.5
Thigh, right	49.5
Thigh, left	49.5
Calf, right	33
Calf, left	33.5
Arm, right	27.5
Arm, left	27.5
Torso-leg ratio	39/82 or .47

LABORATORY DATA

BLOOD

	Feb. 11, 1920	May, 1920
Erythrocytes	4,200,000	4,320,000
Leukocytes	6,700	8,500
Hemoglobin, per cent	90	80
Differential count:		
Small mononuclears, per cent	22	16
Large mononuclears, per cent	8	13
Polymorphonuclears, per cent	70	71

BLOOD CHEMISTRY

Blood sugar (fasting stomach), 0.106 per cent. (106 mg. per 100 c.c. of blood).
Blood sugar (116.9 gm. of glucose given), 0.136 per cent. (136 gm. per 100 c.c. of blood).
Blood urea: 40 mg. per 100 c.c. of blood.
Blood creatinin: 1.875 mg. per 100 c.c. of blood.
Blood calcium: 10.6 mg. per 100 c.c. of blood (Dr. K. M. Vogel).
Blood carbon dioxid: 62.4 volume per cent.
Blood Wassermann reaction negative Jan. 8, 1920, and Feb. 12, 1920.
Bleeding time: 2 minutes.
Coagulation time; 6 minutes.

FECES

March 1, 1920: Color, brown; consistence, medium; mucus, negative; blood, negative; muscle fiber, striated and nonstriated present; fat, present; starch, negative.

March 3, 1920: After the ingestion of 200 gm. fat in the form of butter: Color, brown; consistence, medium; mucous, negative; blood, negative; muscle fiber, none found; fat, present. No appreciable increase over that found on previous examination. Starch, negative.

STOMACH CONTENTS

	Feb. 28, 1920	March 1, 1920
Total acidity	18	34
Combined acidity	3	4
Free hydrochloric acid	0	12
Combined hydrochloric acid	10	18
Lactic acid	Faint trace	Negative
Blood (gross and occult)	Negative	Negative

SPINAL FLUID

Pressure, normal; transparency, slight admixture of blood (technic); cell count, normal, discounting presence of blood; globulin, no material increase; Wassermann, negative. Colloidal gold test, normal curve for preliminary and final curves.

URINE

Numerous urine examinations made at varying intervals revealed: Amber; clear; acid, with a specific gravity varying between 1.026 and 1.036; albumin, sugar, acetone and casts were not found in any of the examinations. No polyuria. Phenolsulphonephthalein showed 45 per cent. output for first hour, 25 per cent. output for second hour, a total of 70 per cent.

SUGAR TOLERANCE TEST (ALIMENTARY GLYCOSURIA)

No glycosuria after 100 gm. glucose, after 180 gm. and after 200 gm. glucose (given in 430 c.c. of milk equaling 30 gm. of lactose).

No glycosuria in the first hour, after 230 gm. glucose (with 1 c.c. of 1:1,000 solution epinephrin given one-half hour later). Glycosuria very positive two hours later; glycosuria less positive three hours after that; glycosuria still less positive four hours later.

After three weeks of thyroid gland feeding (from 6 to 9 grains a day), 100 gm. glucose were given in the morning with no thyroid gland tablets; no glycosuria resulted. On the following morning, 3 grains thyroid gland was given by mouth, followed by 100 gm. glucose in one-half hour; a very faint trace of sugar was noted in the urine collected, following the above procedure.

BASAL METABOLISM

Calories per square meter per hour, 39.9. Variation plus 1 per cent.

ROENTGEN-RAY EXAMINATION

No abnormalities noted in bones and joints; all epiphyses are firmly united.

Fluoroscopic examination shows a rather large stomach with its lower border one inch below the intercristal line. It is slightly hypotonic with no filling defect apparent. The duodenal cap appears to have a filling defect which is inconstant. The ileum is pulled over slightly to the right of the median line. There is no six hours retention. The twenty-four hour plate reveals the barium still in the cecum. The forty-eight hour plate reveals an almost empty intestine. Roentgen findings suggest a large slightly hypotonic stomach with probably periduodenal adhesions; in addition there appears to be some pericecal adhesions.

The chest reveals a slight broadening of the mediastinal shadow (thymus?).

Examination of the skull reveals a small sella turcica with a posterior clinoid process which is definitely thickened. A suggestive pineal shadow is found (Fig. 14).

Hands: The tuft of the left thumb is considerably smaller than that of the right; the other tufts are equal in size, but slightly smaller than usually seen.

ATROPIN TEST

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Respiration	Symptoms and signs
Before administration	44	105	60	20	Pulse shows marked respiratory arrhythmia.
Administration of 1/75 grain					
20 min. later.....	44	90	60	20	No dryness of mucous membrane; respiratory arrythmia less marked.
30 min. later.....	48	95	65	20	Slight dryness of tongue; respiratory arrhythmia almost entirely disappeared.
45 min. later.....	54	95	70	20	Moderate dryness of tongue
1 hour later.....	56	102	65	20	Same.

ERGOTIN TEST

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Signs and Symptoms
Before administration	64	100	70	
Ergotin, 1/10 grain.....	..	...	..	No reaction was noted following this drug.

ESERIN TEST

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic
Before administration	72	105	70
Eserin, 1/50 grain			

Following the administration of this drug, no gastro-intestinal effects were noted, the only reaction was slight headache.

PILOCARPIN TEST

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Respiration	Symptoms and Signs
Before administration	58	100	60	22	
Administration of 0.008 gm.					
10 min. after.....	70	90	55	22	Feels warm; face considerably flushed; slight perspiration.
18 min. after.....	60	100	60	22	Face moderately flushed; considerable perspiration; moderate salivation; a feeling of warmth noted; respiratory arrhythmia unchanged.
24 min. after.....	62	100	60	22	Feels cooler; moderate perspiration; slight salivation; desire to urinate present.
30 min. after.....	62	100	60	22	Feels cool; no salivation; perspiration much less, slight on forehead; face less flushed; temperature, 97.4 F.

PILOCARPIN TEST (REPEATED)

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Signs and Symptoms
Before administration	60	100	65	
Pilocarpin, 1/10 grain				
10 min. after	60	96	60	Moderate flushing of face; slight salivation and moisture of skin; complains of headache.
15 min. later	60	100	60	Skin moderately moist, moderate salivation.
25 min. later	60	100	60	Face moderately flushed, skin moist, salivation fairly marked.
30 min. later	..	...	..	Skin moist, salivation fairly marked; patient exhibited psychic changes after administration of drug; began to cry and stated he was worried over his mother; said he was "bursting with sorrow."

EPINEPHRIN TEST

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Respiration	Signs and Symptoms
Before administration	58	102	70	16	Considerable respiratory arrhythmia.
1 c.c. of 1: 1,000 solution hypodermically					
10 min. later	52	102	70	15	No tremor no general reaction.

PITUITARY TEST

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	Signs and Symptoms
Before administration	64	100	70	
Pituitrin, 1 c.c.				
5 min. later	64	100	70	
10 min. later	64	100	70	Patient pale; desires to urinate.
20 min. later	64	100	70	Desire for defecation present; movement of bowels occurred.

Thermo-reaction (Cushing) negative, i. e., no rise in temperature after injection of pituitrin (1 c.c.).

TYRAMIN

	Pulse	Blood Pressure Systolic	Blood Pressure Diastolic	
Before administration	54	100	60	
Tyramin, 60 mg.				
5 min. later	40	110	64	
12 min. later	44	105	60	Blood pressure rise very slight

Narrow slits; enopthalmos; tendency toward myosis; gag reflex lessened. Oculocardiac phenomenon positive pulse, 64, slowed to 48. Winking infrequent. Epinephrin into conjunctival sac, negative. Goetsch's test (intracutaneous injection of epinephrin) negative.

DISCUSSION

1. *The Endocrine Balance.*—The cretin facies, the enlargement of the thyroid gland, the subnormal temperature, the increased sugar tolerance, the thick skin, the hypotonic vegetative nervous system, and the insensitiveness to large amounts of thyroid gland feeding, are conclusive evidences of a hypothyroidism.

The testicular atrophy reveals the gonadal deficiency.

The parathyroid involvement is suggested by the myotonia (see below) in this connection the occurrence of double cataract in the father at the age of 48 might be construed as a parathyroid defect.

The rôle of the thymus is uncertain.

2. *Myotonia Congenita.*—The association of this remarkable motor disorder with endocrine disturbances has been noted before. W. Falta writes of this relationship under diseases of the parathyroid gland and

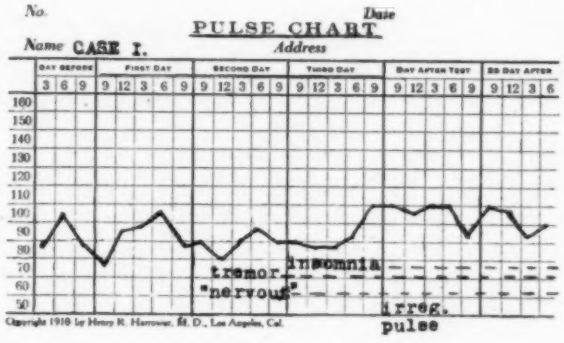

Fig. 15.—The response to ascending doses of thyroid gland (Harrower's test).

notes the presence of myotonia in certain cases of tetany; he states that "just those animals in whom thyroid and parathyroids have been removed show these manifestations," i. e. myotonia. Steinert,[14] speaking of the closely allied myotonia atrophica, emphasizes the atrophy of the testicles and impotence in his cases.

It will be noted that the myotonia in this instance is associated with a very definite thyrogonadal deficiency.

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14. Steinert: Ueber das klinische und anatomische Bild des Muskelschwunds des Myotoniker, Deutsch. Ztschr. f. Nervenh. **37**:58, 1909.

Certain American authors have likewise called attention to the dependence of this myopathy on endocrine disturbances.[15]

3. *Metabolism.*—The essentially normal basal metabolism again demonstrates the fact that the hypothyroidism is compensated for by the activity of the other glands and possibly through the agency of other mechanisms less understood.

As for the calcium metabolism, we have not had the facilities at hand to estimate this, with the detail with which Rosenbloom and Cohoe [16] have accomplished it. These authors concluded from their studies that a "loss of calcium may play a part in the production of the symptoms of myotonia congenita."

The increased sugar tolerance is noted in the alimentary tests. Of interest is the reduction of sugar tolerance with the consequent appearance of a slight glycosuria after the oral administration of three grains of thyroid gland (see laboratory data); this seems to show in a conclusive way the dependence of increased sugar tolerance upon thyroid deficiency in this case.

4. *The Psyche.*—The mental deficiency and inadequate personality reactions present in this case point again to a basic hereditary developmental defect which affects both the psyche and ductless glands.

THERAPEUSIS

For over a period of one month he was given first 6 grains and then 9 grains of thyroid gland a day, together with $\frac{1}{10}$ grain parathyroid gland, three times a day, and potassium iodid, 5 minims, three times a day. Under such therapy there was no appreciable change in the myotonia. Hoffmann (quoted by Falta), in a case of myotonia associated with tetany, noted the disappearance of the myotonia on the administration of thyroid gland and its reappearance after withdrawal, while the tetanic symptoms were not affected.

There was an increased psychomotor activity—purely a quantitative increase, however; the same psychic abnormalities (childish behavior, emotional instability and irresponsibility) were still in evidence. He stated that he had some difficulty in getting asleep, and that he felt warm at night. No tremor, tachycardia, loss of weight or diarrhea occurred, nor were there any changes noted in the configuration of the thyroid gland. A coryza due to the iodid necessitated a discontinuance of this drug for a time.

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15. McCouch, G. P., and Ludlum, S. D. W.: Is Myopathy Related to Disorders of Internal Secretion? Med. Rec. **39**:1042, 1916.

16. Rosenbloom, J., and Cohoe, B. A.: Clinical and Metabolism Studies in a Case of Myotonia Congenita-Thomsen's Disease, Arch. Int. Med. **14**:263 (Aug.) 1914.

CONCLUSIONS

1. Three unusual cases are presented in detail, in each of which remarkable endocrinopathies are associated with unusual manifestations in the muscular system.

2. Attention is directed to the endocrine balance, the sugar and the basal metabolism.

3. It is shown that the basal metabolism is the result of the sum total activities (in part compensatory), of the various ductless glands. In polyglandular disorders, such as those described, the basal metabolism does not reflect the degree of participation of any individual gland.

4. In two cases a congenital developmental defect is postulated as the cause of both the endocrine deficiencies and the psychic disorders.

To Drs. George Draper and Henry E. Marks we owe our especial thanks for most of the laboratory findings, and for valuable advise.

Our thanks are also due to Lieut.-Col. Craig R. Snyder, M. C., U. S. Army, Drs. Karl M. Vogel, H. O. Mosenthal, Emil Baumann, S. P. Goodhart and Walter Timme.

Because of the very generous cooperation of these gentlemen, most of the detailed work was made possible.

BLOOD VOLUME IN PERNICIOUS ANEMIA*

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Blood volume in pernicious anemia has been studied but little, and the results obtained have been at considerable variance. Of the literature concerning blood volume, only that portion bearing on pernicious anemia is considered in this paper. Various methods have been followed, such as the dye method of Keith, Rowntree and Geraghty,[1] the carbon monoxid method of Haldane and Smith [2] and those methods such as Quincke's [3] and Lindeman's,[4] based on the consideration of the red cells before and after transfusion. The dye method of Keith, Rowntree and Geraghty is based on the concentration in the blood of a dye injected intravenously which remains in the circulation for a long time. From this the plasma volume can be calculated and by the hematocrit readings the total blood volume determined. In three determinations made in cases of pernicious anemia they found the total volume in two to be decreased and in the third a normal total volume with a markedly increased plasma volume.

The carbon monoxid method consists in the inhalation by the subject of a known volume of this gas and the determination of its percentage saturation in the blood. From this the total capacity of the blood for carbon monoxid can be found and this is synonymous with total oxygen capacity. It can possibly be best explained by an example. A patient having absorbed 100 c.c. of carbon monoxid, it is found that his blood is 20 per cent. saturated by this gas. The total capacity, then, for carbon monoxid is 500 c.c. and as the oxygen capacity is the same as that of carbon monoxid, that is likewise 500 c.c. The oxygen capacity of the patient determined previous to the administration of carbon monoxid is 20 per cent. The total blood volume is calculated as follows:

$$\frac{500}{20} \times \frac{100}{} = 2,500$$

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* From the Medical Clinic of the Peter Bent Brigham Hospital, and the Harvard Medical School. This is Study No. 12 of a series of studies on the Physiology and Pathology of the Blood from the Harvard Medical School and allied hospitals.

1. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: Arch. Int. Med. **16**: 547 (Oct.) 1915.
2. Haldane, J., and Smith, J. L.: J. Physiol. **25**:331, 1899.
3. Quincke, H.: Deutsch. Arch. f. klin. Med. **20**:27, 1877.
4. Lindeman, E.: J. A. M. A. **70**:1209 (April 27) 1918; ibid., 1292.

This method was used in the study of pernicious anemia by Lorraine Smith,[5] who found that the total amount of hemoglobin was reduced in proportion to the severity of the disease and that the plasma might either be increased or diminished. He concluded that those patients with increased total volume were worse symptomatically than those with a more concentrated blood.

Quincke's and Lindeman's methods depend on the changes produced by transfusion in the number of red cells. Quincke calculated blood volume from the red count of the donor's blood and the amount given. The red count is not sufficiently accurate to give good results.

Lindeman centrifuged equal specimens of the donor's blood and that of the patient before and after transfusion of large amounts of blood. The principle is the same as that of Quincke but the results are more accurate. He found the blood volume in pernicious anemia to be always reduced but more in some cases than in others, and concluded that when the total volume is only slightly reduced the symptoms are fewer though the relative anemia be severe. This conclusion as to the relation of symptoms to volume is in absolute variance with that of Lorraine Smith.

It is obvious that if we had any one element in the blood which we could determine with absolute accuracy, the blood volume could be measured by the change in concentration of that element produced by transfusion. This would be true provided vaso-motor changes produced by the transfusion were not of any great extent. In the present study, I have used the oxygen capacity of the blood, as it most nearly represents the ideal of an element which can be measured accurately. The method is simply the determination of the oxygen capacity of the patient's blood immediately before and three minutes after the completion of the transfusion. The oxygen capacity of the citrated blood of the donor is determined and from these three factors and the volume of blood given, the total blood volume is calculated as follows:

A = oxygen capacity of patient's blood before transfusion.
B = oxygen capacity of patient's blood after transfusion.
D = oxygen capacity of the citrated blood administered.
Q = quantity given in cubic centimeters.

$$V = \frac{D - B}{B - A} \times Q$$

Oxygen determinations were made with the Van Slyke blood gas pump.[6] The blood sample taken before transfusion was obtained from

5. Smith, J. L.: Tr. Physiol. Soc. London **51**:311, 1900.
6. Van Slyke, D. D.: J. Biol. Chem. **33**:127, 1918.

the needle through which the blood was subsequently given. That taken after was obtained from the opposite arm two or three minutes after the last of the blood had been introduced. About 500 c.c. of blood was usually given.

In order to test the accuracy of this method a few experiments were done on blood in vitro. The oxygen capacity of sheep's blood was determined, salt solution added (about 10 per cent. of the total amount of blood), and the oxygen capacity redetermined.

PROTOCOLS OF EXPERIMENT

EXPERIMENT 1.—Sheep's blood, 226 c.c., to which (Q) 22 c.c. of normal salt solution was added; (A) oxygen capacity before addition = 24.66; (B) oxygen capacity after addition = 22.36. The formula for a simple dilution such as this is $\frac{V}{V+Q} = \frac{B}{A}$.

$$\frac{V}{V+22} = \frac{22.36}{24.66}$$

$$24.66\ V = 22.36\ V + 491.92$$
$$2.30\ V = 491.92$$
$$V = 214 \text{ c.c.}$$

Error about 5 per cent.

EXPERIMENT 2.—457 c.c. sheep's blood. (A) Oxygen capacity = 18.97 per cent. Forty-five c.c. salt solution added. (B) Oxygen capacity = 17.15 per cent.

$$\frac{V}{V+45} = \frac{17.15}{18.97}$$

$$18.97\ V = 17.15\ V + 771.75$$
$$1.82\ V + 771.75$$
$$V = 424 \text{ c.c.}$$

Error, 7 per cent. minus.

EXPERIMENT 3.—450 c.c. sheep's blood. (A) Oxygen capacity = 19.26 per cent. Forty-five c.c. physiologic sodium chlorid solution added. (B) Oxygen capacity = 17.46 per cent.

$$\frac{V}{V+45} = \frac{17.46}{19.26}$$
$$V = 437 \text{ c.c.}$$

Error, 3 per cent. minus.

Blood from a patient suffering from congenital heart disease with polycythemia was used in a further set of experiments in vitro. In this case the blood was diluted to represent an anemia and transfusion done in the test tube with the usual oxygen determinations made on the various samples.

EXPERIMENT 4.—(A) 490 c.c. of diluted blood with an oxygen capacity of 10.59 per cent.

(D) To the above 45 c.c. of blood with an oxygen capacity of 32.62 per cent. was added.

(B) Oxygen capacity of the mixture = 12.37 per cent.

$$V = \frac{32.62}{12.37} - \frac{12.37}{10.59} = 45$$

$V = 512$

Correct $V = 490$.

Error, 4 per cent. plus.

(A) 500 c.c. diluted blood with an oxygen capacity of 4.85 per cent.

(D) To this 50 c.c. of blood with an oxygen capacity of 19.19 per cent. was added.

(B) Oxygen capacity of this mixture is 6.01 per cent.

$V = 568$ c.c. Should be 500 c.c., an error of 13 per cent. plus. This error was thought to be due to insufficient addition of normal blood, so the experiment was continued.

(A) To 452 c.c. of diluted blood with an oxygen capacity of 6.01 per cent.

(D) 70 c.c. of blood added having an oxygen capacity of 19.19 per cent.

(B) Oxygen capacity of the mixture is 7.86 per cent.

$$V = \frac{19.19}{7.86} - \frac{7.86}{6.01} \times \frac{70}{} = 430 \text{ c.c.}$$

It should be 452 c.c., making an error of about 5 per cent. minus.

From these test tube experiments with dilution and concentration of blood it is seen that the changes produced in oxygen capacity are sufficient to give a fairly accurate determination of volume. To a dilute blood at least 10 per cent. of a normal blood must be added in order to produce changes in the oxygen capacity which are sufficient to permit calculation of the volume.

The total blood volume of ten patients who were transfused for pernicious anemia was determined by the method described. Also, for comparison, their total blood volume was calculated on the basis of the body weight which, according to Keith and Rowntree's figures for the normal, is 85 c.c. of whole blood per kilo body weight. This is referred to as the theoretical volume.

REPORT OF CASES

CASE 1 (Med. No. 11710).—H. H. McK., aged 42, clerk, married. Diagnosis: pernicious anemia.

Patient entered hospital Sept. 18, 1919, complaining of weakness. During the last three years patient has had periods of weakness lasting from one to two months, some of which prevented him working. Three months ago he had a much more severe attack, during which he lost all appetite and was forced to stop work. Numbness of hands present for last six or seven weeks. Gradually getting pale. Weight three months ago, 62 kg.

Physical examination shows little but lemon yellow pallor, irregular pupils which react, a smooth glistening tongue, and a palpable liver. Gastric analysis shows anacidity. Blood smear typical of primary anemia. No nucleated forms.

Transfused September 24 with 500 c.c. citrated blood having an oxygen capacity of 18.89 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	6.13%	33%	980,000
After transfusion.....	7.92%	42%	1,440,000

Total blood volume = 3,064 c.c.
Theoretical volume = 4,541 c.c.

Transfused October 7 with 510 c.c. of citrated blood having an oxygen capacity of 20.89 per cent. Some blood spilled so figures are not accurate. This illustrates the fact that small errors may make a large difference in the result.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	9.65%	52%	1,480,000
After transfusion.....	11.85%	64%	2,300,000

Total blood volume = 2,095 c.c. Weight unchanged.

Transfused October 14 with 560 c.c. of citrated blood having an oxygen capacity of 21.66 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	13.24%	71.6%	2,424,000
After transfusion.....	14.57%	78.8%	2,660,000

Total blood volume = 2,985 c.c.

Patient left the hospital considerably improved and could do a fair amount of walking without palpitation or dyspnea. Reentered December 14 with practically all the complaints of his first admission. No edema noted.

Transfused December 18 with 475 c.c. of citrated blood having an oxygen capacity of 20.46 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	4.90%	26%	1,300,000
After transfusion.....	7.08%	38%	1,600,000

Total blood volume = 2,915 c.c.

Transfused January 6 with 510 c.c. of citrated blood having an oxygen capacity of 20.43 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	7.60%	40%	1,766,000
After transfusion.....	9.20%	49%	2,244,000

Total blood volume = 3,548 c.c.

Assuming that the volume calculated was correct, the proportion of donor's blood to the patient's can easily be figured. In the determination of December 18, it is 1:6.13, and in that of January 6 it is 1:696. If, then, the blood of the donor and that of the recipient are mixed in the test tube in these proportions, an oxygen capacity identical with that found after transfusion should result provided the volume is correct. This was done and the following results were obtained:

	Dec. 18	Jan. 6
Oxygen capacity after transfusion.....	7.08%	9.20%
Oxygen capacity of the test tube mixture..	7.08%	9.20%

Furthermore, January 6 the theoretical volume on the basis of 85 c.c. per kilo body weight was calculated and found to be 4,590 c.c. If this were the true volume, the proportion of donor's blood to that

of the recipient would be 1 : 9. Such a mixture was made and a reading of 8.52 per cent. oxygen capacity obtained, thus showing that the volume must be considerably less than the calculated normal of Keith and Rowntree.

CASE 2 (Med. No. 11799).—G. K., aged 53, clerk; entered hospital Nov. 24, 1919, complaining of weakness. Lived in China for thirty years and contracted sprue five years ago since when he has had severe diarrhea controlled more or less by santonin. Weight five years ago, 214 pounds; present weight, 135 pounds. Has lost 10 pounds in the last three months. Seven months ago had three intravenous arsphenamin injections for sprue, following which he became very weak, jaundiced and anemic. Diarrhea continued. Physical examination negative, except for yellowish pallor, small fresh hemorrhage in fundus of left eye. Tongue pale; smooth. Abdomen slightly distended, but liver and spleen not palpable. No edema. No free hydrochloric acid in gastric contents. Severe and persistent diarrhea, with from three to ten stools per day.

Transfused October 3 with 460 c.c. of citrated blood having an oxygen capacity of 20.92 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	10.19%	54%	1,620,000
After transfusion.....	11.08%	59%	Not done

Total blood volume = 5,086 c.c.
Theoretical volume = 4,879 c.c.

Transfused October 17 with 550 c.c. of citrated blood having an oxygen capacity of 22.55 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	10.12%	54%	1,520,000
After transfusion.....	11.45%	61%	2,160,000

Total blood volume = 4,588 c.c.

Transfused October 24 with 612 c.c. of citrated blood having an oxygen capacity of 23.18 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	12.11%	65%	2,220,000
After transfusion.....	13.92%	75%	2,540,000

Total blood volume = 3,131 c.c.

During the period between October 17 and October 24, there was an intense diarrhea which might account for some lowering of blood volume; however, this last volume being so much lower, was checked in the test tube by adding donor's blood to recipient's blood in the proportion calculated from the volume; namely, 1 : 5.11. This gave a reading of 14.32 per cent. instead of 13.92 per cent. oxygen capacity, thus showing that the volume is too low. A mixture was then made in the proportion of 1 c.c. of donor's blood to 8.8 c.c. of the recipient's before transfusion, which proportion is based on a volume calculated on the basis of body weight, 5,440 c.c. This gives a reading of 13.03 per cent. oxygen capacity which is considerably under the figure 13.92 per cent. obtained after transfusion.

CASE 3 (Med. No. 12013).—T. M., aged 49, male; entered the hospital Oct. 11, 1919, complaining of weakness and anemia. One sister has a similar anemia. Onset of present illness was in April, 1919, with palpitation and dyspnea and dizziness. Physical examination negative, except for pallor and characteristic tongue.

Transfused October 14 with 620 c.c. of citrated blood having an oxygen capacity of 23.02 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	5.99%	32%	840,000
After transfusion.....	7.81%	42%	1,360,000

Total blood volume = 5,096 c.c. Weight of patient = 82 kg.
Theoretical volume = 6,960 c.c.

Transfused October 29 with 534 c.c. of citrated blood having an oxygen capacity of 22.61 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	5.36%	29%	Not done
After transfusion.....	7.17%	38%	Not done

Total blood volume = 4,552 c.c.

Patient left the hospital unimproved and died November 18.

CASE 4 (Med. No. 12235).—M. A. P., aged 55, housewife; entered the hospital Nov. 10, 1919, complaining of weakness, palpitation, swelling of the feet, hands and abdomen. She has had two similar attacks which were less severe, the first, three and one-half years ago, and the second about ten months later, both of which were less severe than the present attack. Last illness began nine months ago and for the last few months there has been a gradual increase in edema. Physical examination shows typical pallor and tongue and a general anasarca.

Transfused November 14 with 358 c.c. of citrated blood having an oxygen capacity of 19.92 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	10.31%	55%	1,370,000
After transfusion.....	11.70%	62%	1,640,000

Total blood volume = 2,117 c.c.
Theoretical volume = 3,485 c.c. (Calculated on body weight after loss of edema.)

A mixture of the donor's blood and that of the patient before transfusion in the proportion found from the volume gives a reading of 11.34 per cent. oxygen capacity in place of 11.70 per cent. This indicates that the volume calculated is too low.

Transfused November 25 with 508 c.c. of citrated blood having an oxygen capacity of 18.71 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	6.68%	36%	1,750,000
After transfusion.....	8.49%	45%	1,950,000

Total blood volume = 2,870 c.c.

A mixture of donor's and patient's blood in the proportion obtained from this volume gives a reading of 8.49 per cent. oxygen capacity. It is of interest that during the time between the two transfusions the patient lost about 4 kg. of her edema which loss continued until it was all gone. The total loss was 17 kg. At the time of the second transfusion she was clinically improved although her blood shows a distinct falling off in hemoglobin percentage. The increase in volume may be due to a fluid entering the blood with a consequent dilution.

CASE 5 (Med. No. 11111).—J. A., aged 58. Diagnosis: pernicious anemia. Entered hospital with symptoms of weakness, dizziness and dyspnea dating back three months. At this time he showed a typical picture of pernicious anemia. He had a spontaneous remission and was well up to April, 1910, when the old symptoms began to recur. Weakness and pallor are now his principal complaints.

Transfused June 3 with 710 c.c. of citrated blood having an oxygen capacity of 18.05 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	6.36%	34%	808,000
After transfusion.....	8.74%	47%	1,464,000

Total volume = 2,780 c.c. Weight of patient = 51.6 kg.
Theoretical volume = 4,386 c.c.

Case 6 (Med. No. 11822).—R. F., aged 58, housewife. Diagnosis: pernicious anemia. Entered hospital Sept. 11, 1919, complaining of weakness, ringing in the ears and dyspnea. Two years ago she noticed weakness and pallor and loss of weight. This has increased gradually and for the last four months she has had palpitation and dyspnea. Physical examination shows typical pallor, smooth tongue, an enlarged heart and a systolic murmur. The spleen is palpable. No free hydrochloric acid in stomach contents.

Transfused September 26 with 510 c.c. of citrated blood having an oxygen capacity of 19.23 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	7.64%	41%	1,500,000
After transfusion.....	9.03%	48%	2,200,000

Total blood volume = 3,742 c.c. Weight of patient, 58.2 kg.
Theoretical volume = 4,947 c.c.
Discharged greatly improved.

Case 7 (Med. No. 12208).—C. A. L., aged 56, housewife. Diagnosis: pernicious anemia. Entered hospital Sept. 11, 1919, complaining of weakness and anemia. Onset was seven years ago with weakness as the principal symptom. She has had several remissions during this time and for the last few months has noticed pallor, abdominal distress, dyspnea and marked weakness. Physical examination showed yellow pallor, heart slightly enlarged, liver and spleen palpable, tongue smooth. Gastro-intestinal roentgenograms negative. Free hydrochloric acid absent in stomach contents. Blood picture typical of pernicious anemia.

Transfused November 10 with 491 c.c. of citrated blood having an oxygen capacity of 21.02 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	5.81%	31%	2,780,000
After transfusion.....	7.65%	41%	2,830,000

Total blood volume = 3,568 c.c. Patient's weight, 50 kg.
Theoretical volume = 4,250 c.c.

A mixture of donor's blood and that of the patient made in a test tube in the proportion of 1:7.26 which is the relation of the two provided the volume calculated is correct. This mixture has an oxygen capacity of 7.88 per cent. in place of 7.65 per cent., the amount found after transfusion. This would indicate that the true volume is slightly higher than the one calculated.

Patient discharged unimproved.

Case 8 (Med. No. 12313).—A. S. P., aged 61, clerk. Diagnosis: pernicious anemia. Entered hospital Nov. 20, 1919, complaining of weakness, anemia and swelling of legs. Two and one-half years ago had an attack of anemia and weakness lasting six weeks, and another similar attack one year ago lasting two months. He was well and at work between attacks and up to June, 1919, when symptoms reappeared in a more severe form with edema and dyspnea. At entrance, he shows a marked edema of the extremities with fluid in both pleural cavities and abdomen, a yellow pallor of the skin and smooth glossy tongue.

Transfused December 3 with 600 c.c. of citrated blood having an oxygen capacity of 21.74 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	4.43%	24%	908,000
After transfusion.....	6.74%	36%	.....

Total blood volume = 3,900 c.c. Patient's weight, 68 kg.
Theoretical volume = 5,780 c.c.

CASE 9 (Med. No. 2322).—M. C., aged 50, housewife; entered hospital Nov. 21, 1919, complaining of weakness. Onset about one year ago with weakness, dyspnea and palpitation. Has run down steadily, but except for loss of appetite and weight there have been no further symptoms. Physical examination shows typical pallor, a smooth but not glossy tongue and a palpable spleen. There is anacidity of the gastric contents and a blood picture typical of primary anemia. Weight three years ago, 195 pounds; present weight, 134 pounds.

Transfused November 25 with 528 c.c. of citrated blood having an oxygen capacity of 17 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	8.88%	48%	1,880,000
After transfusion.....	10.01%	54%	2,030,000

Total blood volume = 5,280 c.c. Patient's weight, 61 kg.
Theoretical volume = 5,185 c.c.

CASE 10 (Med. No. 10324).—M. C., aged 50; entered the hospital Dec. 19, 1919, complaining of dyspnea and anemia. Onset of symptoms about January, 1918. These consisted of weakness, pallor and dyspnea on exertion. Has been transfused several times and had two definite periods of improvement during the first of which his blood reached normal. For two months before his present admission all the symptoms have been worse and edema of the legs and epigastric distress are marked. Physical examination shows typical pallor, tongue and blood picture. There is anacidity of the gastric contents, also ascites and edema of the legs.

Transfused January 10 with 521 c.c. of citrated blood having an oxygen capacity of 21.15 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	7.99%	43%	1,048,000
After transfusion.....	9.35%	50%	1,272,000

Total blood volume = 5,742 c.c.

Transfused January 15 with 495 c.c. of citrated blood having an oxygen capacity of 19.94 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	7.03%	37%	1,275,000
After transfusion.....	8.16%	44%	1,808,000

Total blood volume = 5,160 c.c. Patient's weight, 59 kg.
Theoretical volume = 5,015 c.c.

RELATION OF PLASMA AND CELLS

Hematocrit determinations were done in most of the cases and in the following table the results are given expressed in cubic centimeters per kilo body weight.

It is quite evident that the reduction in total volume is due to the decrease of red cells rather than to any change in plasma volume. Cases 9 and 10 show a normal total volume and in one of these in which the hematocrit determinations were made, the normal volume

is shown to be due to an increase of plasma. This is in conformity with the findings of Keith, Rowntree and Geraghty. The average plasma volume is, however, normal. Case 9 shows a high volume per kilo and Case 4 the lowest. The degree of anemia in the two cases was essentially the same. Case 4 had a general anasarca which was diminishing rapidly and Case 2 a very severe and persistent diarrhea.

RESULTS OF HEMATOCRIT DETERMINATIONS IN TEN CASES

Case	C.c. Blood Per Kg. Body Weight	C.c. Plasma Per Kg. Body Weight	C.c. Cells Per Kg. Body Weight
1	56	45	11
2	72	59.5	12.5
3	62	56	6
4	52	46.5	5.5
5	54	Not done	Not done
6	64	Not done	Not done
7	71	60.5	10.5
8	57	50	7
9	88	75.5	12.5
10	86	Not done	Not done
Average	66	56	10
Average normal	85	50	35

SUMMARY AND CONCLUSIONS

1. A method for calculation of blood volume is described.

2. By this method nineteen determinations were made in ten cases of pernicious anemia.

3. The total blood volume in these cases was reduced in all but two cases.

4. Plasma volume remains essentially normal, the decrease in total volume being due to loss of cell mass.

5. The case showing a normal total volume has a high plasma volume.

6. There is no noticeable relation between the severity of the disease and the decrease in total volume.

A SIMPLE DEVICE FOR MEASURING RATE OF METABOLISM *

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Of those laboratory tests useful in the diagnosis of certain forms of disease, perhaps none is more valuable to the clinician than the recent test devised to measure basal metabolism.

The sudden interest which the test has stimulated among clinicians has spread with surprising rapidity, perhaps for the reason that, from the standpoint of efficiency in the differentiation of certain disease, its results are so spectacular in uniformity and conclusiveness. Moreover, it was just this rapid spread of interest in the test which has so effectually confirmed its usefulness as a diagnostic aid. The question as to its value, so far, has been singularly free from controversy.

Lusk [1] and his associates, on the basis of very accurate and elaborate measurements, have emphasized chiefly the scientific aspects of the test.

The problem of making the test available to those clinicians not having access to the elaborate equipment of the nutritions laboratory was solved by Benedict,[2] who designed a portable apparatus for measuring the basal metabolism of human subjects, and by DuBois,[3] who has devised a "linear formula" for use in indirect respiration calorimetry.

In a recent article, McCaskey [4] says of the method originated by Benedict: "Unless its clinical value can be shown to be commensurate with the time, labor and equipment required, and in this instance these items are rather large, it cannot and should not endure." His paper is offered as an additional contribution to this end. In other words, he believes that the urgent need for such a test justifies the fairly considerable expenditure of time, labor and equipment necessary to its performance.

To extend still further its usefulness by reducing to a minimum this expenditure of time, labor and equipment, I undertook to devise an apparatus which is simple and accurate in operation and yet sufficiently compact for the surgeon, clinician or general practitioner to carry it to the patient's home or bedside, an apparatus which is portable in a practical sense. In designing it, I have kept this feature constantly in mind.

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* From the Department of Pathology and Bacteriology, University of Illinois College of Medicine.

1. Lusk: Arch. Int. Med. **15**:793 (May) 1915.
2. Benedict: Boston M. & S. J. **178**:667, 1918.
3. DuBois: Arch. Int. Med. **15**:793 (May) 1915; **17**:855 (June) 1916.
4. McCaskey: J. A. M. A. **74**:927 (April) 1920.

A second feature also deserves special emphasis in this connection. All mathematical computations have been eliminated. The units expressing the results of the test are arrived at immediately and without calculation. A method which involves the use of logarithms, slide rule and considerable time for calculations, as in the case of the Benedict method, has not properly considered the inability of the average busy clinician to deal with this kind of mathematical procedure.

PRINCIPLE OF THE METHOD

The ratio of the quantity of carbon dioxid eliminated to the quantity of oxygen consumed is called the respiratory quotient. In the oxidation of fat this R Q (respiratory quotient) is about 70: 100, or 0.70; of carbohydrate it is 100: 100, or 1. Obviously, when a combination of fat and carbohydrate is oxidized, the R Q lies somewhere between 0.70 and 1. It is necessary to know the R Q because the

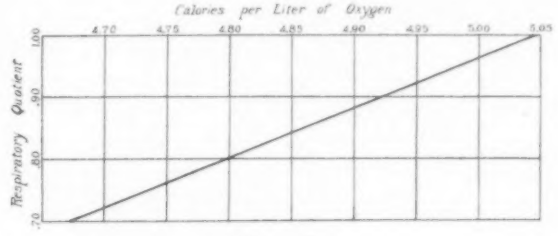

Figure 1.

caloric value of a liter of oxygen, a factor which must be known, varies with the R Q, as shown in Figure 1.

With appropriate apparatus, the determination of the R Q, i. e., the amount of carbon dioxid eliminated and oxygen consumed, is an ordinary laboratory procedure. Having determined the R Q, reference to Figure 1 gives the caloric value of each liter of oxygen so consumed. The number of liters of oxygen consumed,[5] multiplied by the caloric value of one liter at this R Q then gives the total caloric radiation or rate of metabolism.

In figure 1 it is seen that the caloric value of oxygen is not markedly affected by varying the value R Q. In fact, in clinical work, it is

5. A measure of the carbon dioxid eliminated could also be made the basis for calculating the heat output according to this same reasoning. The objections to this method, however, are that the caloric value represented by the elimination of a liter of carbon dioxid varies too widely, depending on whether it was derived from the burning of fat or of carbohydrate, and also to the fact that irregularities in the respiration causing overventilation of the lungs increase this error in determinations extending over such short periods.

customary to assume the R Q as 0.82, which has been found to be the average of a large number of determinations. By so doing, the task of measuring the carbon dioxid to ascertain the ratio is obviated, and it is necessary then only to measure the oxygen intake.

To calculate the caloric output by measuring the rate of oxygen intake and multiplying this by the caloric value of one liter at the assumed R Q of 0.82 is, therefore, the principle on which the apparatus here described is designed to operate.

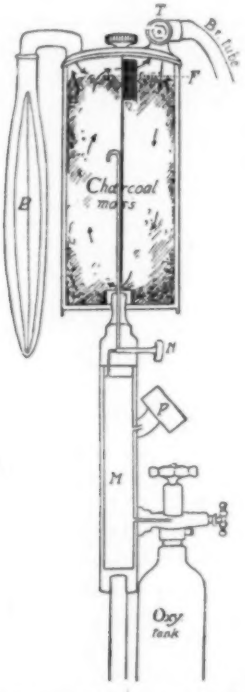

Fig. 2.—Cross-section of apparatus: Arrows indicate direction of movement of inspired and expired air; Br. tube, breathing tube; T, three-way cock; F, flutter valve for directing circulation of gases; b, rubber bag to contain measured amount of gas and to allow for expansions and contractions in respiration; N, needle valve for releasing the measured amount of oxygen from M, the measuring cylinder, into the charcoal-alkali tower above; P, pressure gauge with room temperature scale on dial to indicate when one liter of dry oxygen at 0 C. and 760 mm. has been released at any given room temperature from the oxygen tank.

CLINICAL APPLICATION OF THE METHOD

There are three principal ways in which the living body expends its store of heat. 1. Following the ingestion of food there is a marked

rise in the rate of heat loss due to the specific dynamic action of foods. 2. Muscular exertion requires an expenditure of its caloric equivalent. Its effect on the heat loss ceases with complete muscular relaxation usually within thirty minutes following ordinary muscular effort. 3. Certain vital processes, such as respiration, circulation, secretion, the maintenance of body temperature, etc., must be supported irrespective of the first two and at the expense of the food stores or tissues of the body.

The first two represent variable quantities and may be eliminated by fasting and muscular relaxation, as indicated above. However, the third is a remarkably constant quantity for a given individual. Ordinarily this regular and ever present demand for the maintenance of the vital functions amounts to more than one-half of the body's daily expenditure of heat; and because of the constancy with which it takes this toll, even in conditions of extreme starvation it has been given the name basal metabolism.

Under conditions of basal metabolism, the rate of heat loss of different individuals is surprisingly similar. It varies with sex and age, being higher in youth and in males, but these factors need only to be taken into account to determine what is normal in any given case. So true is this, that when the basal metabolism of a given individual varies more than 10 per cent. from the normal for that patient's sex and age, certain diseases may be diagnosed on the basis of this change from the normal rate.

DESCRIPTION OF THE APPARATUS

The apparatus (Fig. 2) consists merely of a mouthpiece with wide flexible tube leading the expired air into the apparatus; a tower of small pieces of charcoal, soaked in alkali, for the purpose of removing the carbon dioxid; a gas anesthetic rubber bag to allow for expiration and inspiration and to contain the oxygen supply; a piece of aluminum pipe serving as a support to the alkali tower, and also as a measuring apparatus for delivering into the rubber bag a known quantity of oxygen. The measuring cylinder is also provided with an attachment for the small forty gallon oxygen cylinder, and with a pressure gage with special dial to indicate when the desired quantity of oxygen has been released.

The instructions which have been found to cover the points in technic and principle of the method sufficiently to enable one of ordinary skill to carry out the test are as follows:

PREPARATION OF THE PATIENT

(1) Have subject take no food (nothing but water), for from fourteen to eighteen hours previous to test, preferably from 6 o'clock evening meal, to 10 o'clock next morning, when test is made.

(2) Subject should be lying comfortably and quietly from fifteen to thirty minutes before test begins.

TECHNIC OF THE TEST

Attach nose clip and test for air leak at nose by having subject close mouth and exert moderate pressure. Turn three-way cock open to air. Insert rubber shield of mouth piece inside of lips but outside of teeth, drawing lips up about neck of mouth piece. Open needle valve of measuring cylinder. Admit gas slowly from oxygen tank until bag distends sufficiently to just touch the side of the alkali tower. This quantity is used merely to establish what is called the *beginning point.* Now *close* needle valve. Admit gas *slowly* again

Fig. 3.—Apparatus in use.

from oxygen tank while indicator is driven around, and, after tapping gage with finger, stands exactly over room temperature point of scale on dial. When released, later, this quantity will be 1,000 c.c. (± 2 c.c.) of gas at 0 C. and 760 mm. Hg. It is held in the measuring cylinder ready for release at the *beginning point.* Approximately at *beginning of expiration* quickly turn three-way cock closed. Subject is now breathing gases confined in the tower and bag. Observe the quantity of gas in bag as it gradually diminishes in volume. Watch point where bag makes contact with the side of alkali tower. That expiration, when the bag, at its fullest distention, just fails to touch the side of alkali tower, is counted *one.* If the expiration following this one fails to cause the bag to touch the alkali tower it is counted *two;* and the one following this *three.* This establishes the *beginning point.* At this instant release

the stop watch and then discharge the 1,000 c.c. of gas now in measuring cylinder by opening needle valve. *Close* needle valve again and admit a second liter of gas into measuring cylinder. After a few minutes bag will have again diminished in volume to same condition described for the beginning point (namely, three successive normal expirations, when the bag, at its fullest distention, just fails to touch side of alkali tower). Watch for this as before, and when it occurs note time by stop watch. Release second liter to bag, as before. Close needle valve again and admit a third liter to measuring cylinder. Proceed in this way, observing exact time required by subject to consume each successive liter. Two liters is usually sufficient but average of three is better. Finally at the end point of the last liter used, stop the watch, turn three-way cock to open, and remove the mouth piece. Before removing nose clip, test again for air leaks as at beginning of test. (If air leak has developed during test discard the readings.) Total time on watch divided by number of liters consumed equals *average time required to consume one liter*, and from this the subject's rate of metabolism is made known as follows:

TO CALCULATE METABOLIC RATE

To illustrate: Male, age, 30; height, 66 inches; nude weight, 153 pounds; averaged 3.1 minutes to consume 1 liter of oxygen. Referring to Table 1, his height and weight lines intersect in a point between oblique lines 1.7 and 1.8, say at 1.79; 1.79 square meters is, therefore, his body-area. Referring to Table 2, this body-area line, 1.79, and his 3.1 minute line, intersect in a point between 50 and 55, say 53. Rate is, therefore, 53 calories per square meter per hour or + 34 per cent., i. e., 34 per cent. above the normal for his age and sex, as seen from Table 3.

CARE OF ALKALI TOWER

Pour about 400 c.c. of a *saturated* solution of commercial sodium hydrate over coal mass. About 100 c.c. of this will settle to bottom. A few minutes before beginning on a test, hold back coal particles with hand and drain this bottom fluid into a glass or beaker, then pour it over coal mass again to redistribute the alkali. Run the test and duplicate test, then drain this bottom liquid off again and discard it. For another test and duplicate test use another fresh 100 c.c. portion of the alkali solution. After test, drain and discard as before. Before putting apparatus away always drain off this bottom fluid, and then pour in about 200 c.c. water to wash off the exhausted alkali on the coal particles. Drain this off, and then pour in another 200 c.c. water to stand in bottom of tower until used again. This prevents crystallization of sodium bicarbonate in bottom and clogging of coal mass. Before using apparatus again, drain this water off and pour on about 100 c.c. of saturated solution of sodium hydrate, which will be sufficient for a test, and duplicate test, as before.

The height-weight table (Fig. 4) is modified after the table of DuBois [8] according to his "linear formula": Area = W 0.425 × H 0.725 × 71.84.

The body area-minute table (Fig. 2) is constructed according to the formula $\frac{4.823 \times \text{liters of oxygen consumed per hour}}{\text{Surface area of patient}} =$ calories per hour per square meter, in which 4.823 is the caloric value of one liter oxygen at the assumed R Q 0.82, and in which the liters of oxygen consumed per hour was calculated on the basis of the average number of minutes required by the patient to consume one liter of oxygen.

SOURCES OF VARIATIONS

1. *Age and Sex.*—The effect of age and sex on the rate of metabolism is shown in Table 1 by Aub and DuBois.[6]

TABLE 1.—VARIATIONS DUE TO AGE AND SEX, EXPRESSED AS CALORIES PER SQUARE METER PER HOUR

Age	Males	Females
14–16	46.0	43.0
16–18	43.0	40.0
18–20	41.0	38.0
20–30	39.5	37.5
30–40	39.5	36.5
40–50	38.5	36.0
50–60	37.5	35.0
60–70	36.5	34.0
70–80	35.5	33.0

In expressing the rate of metabolism as ±%, the above factors must therefore be taken into account.

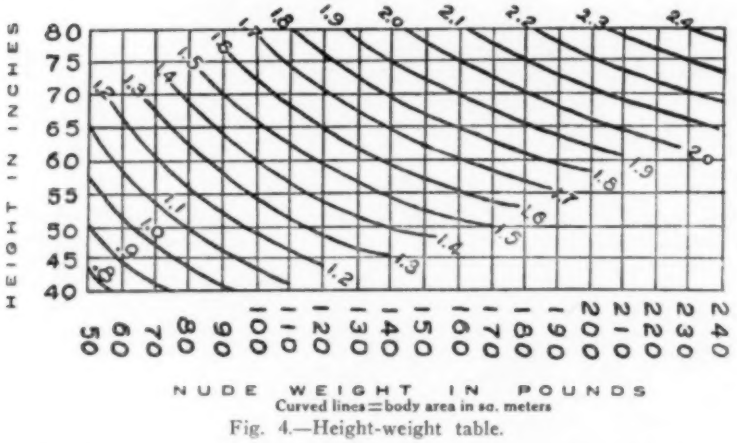

Fig. 4.—Height-weight table.

2. *The Effect of Foods.*—The specific dynamic action of food may be defined as that effect which the ingestion of food has in stimulating the metabolic rate to an increase above the basal rate. For proteins this stimulating action amounts to an increase of 33 per cent. of the caloric value of the amount of protein ingested; for fats it is 11 per cent, for carbohydrates, 5 per cent. The patient is instructed to take no food after the six o'clock evening meal, the test being made at about 10 o'clock the next morning, i. e., sixteen hours after the last meal. If these instructions are not made clear, or the subject forgets, or uses deception in regard to them, this specific dynamic action of food enters as a source of considerable variation, and may take the observer unawares. Another source of error which may also

6. Aub and DuBois: Arch. Int. Med. **19**:831 (July) 1917.

take the observer by surprise is that due to the effect of caffein [7] in increasing the rate of metabolism. If the patient is allowed his morning cup of coffee or tea on the assumption that it contains nothing of any food value, the observer is then at a loss to explain the 10 or 20 per cent. rise above the normal basal rate.

3. *Muscular Tension and Psychic States.*—The effect of muscular tension in increasing the rate of metabolism is obvious. If the subject is restless, or lies in an uncomfortable or tense position, or is subjected to various psychic disturbances as fear of the test, or embarrassment, the effect in increasing the metabolism above the basal rate may be even greater than in the last mentioned source of variation. For example, in a demonstration of this apparatus given before the Chicago Society of Internal Medicine, the subject's rate rose to 28 per cent. above her basal rate; which later, under less exciting conditions, was normal. In spite of her attempts to assume complete muscular relaxation, the rate of metabolism, more than anything else, revealed the attack of stage fright, which the subject later admitted. Some day the criminologist, by the aid of appropriate controls and setting, may find in this stimulating action of fear a dependable ally in the detection of crime. The point of therapeutic value is that a patient, put to bed to reduce his rate of metabolism, defeats the purpose in a large measure, sometimes by worry, by homesickness, by entertaining visitors, or by a number of other ways in which the psychic element has not been considered.

4. *Variations Due to Certain Diseases.*—When the basal rate of metabolism of a subject is found to be constantly above or below the average basal rate for persons of his age and sex, certain diseases are diagnosed, chief among which are disturbed functions of the thyroid and pituitary. Severity of the disturbance is proportional to the variation from the normal rate, and, therefore, by following the variation of the rate from the normal by successive tests, the effect of therapy can be demonstrated. Following the effect of treatment is, in fact, one of the firmly established uses of the test.

TECHNICAL SOURCES OF VARIATIONS

THE GAS MEASURING APPARATUS: The purpose of the pressure gage is to indicate that pressure at which the measuring cylinder will deliver 1,000 c.c. of dry oxygen at 0 C. and 760 mm. Hg pressure. This volume at 23 C. and 750 mm. Hg becomes 1,098.8 c.c.; if measured over water it is further increased to about 1,128.8 c.c. since the vapor tension at 23 C. is 21 mm. Hg. In operation, however, this

7. Means, Aub and DuBois: Arch. Int. Med. **19**:832 (July) 1917.

measuring apparatus is independent of temperature and pressure changes. The influence of temperature on the gas volume is eliminated by having the pointer of the gage come to rest over various points on the dial representing various room temperatures. The construction of the measuring apparatus is essential in principle to that of the anaeroid barometer, and is, therefore, independent of changes in atmospheric pressure, i. e., the indicator merely represents the tension of gas inside the cylinder as against the tension outside of it, regardless of what this outside tension may be. In spite of these features, the apparatus is not a delicate mechanism requiring frequent readjustment

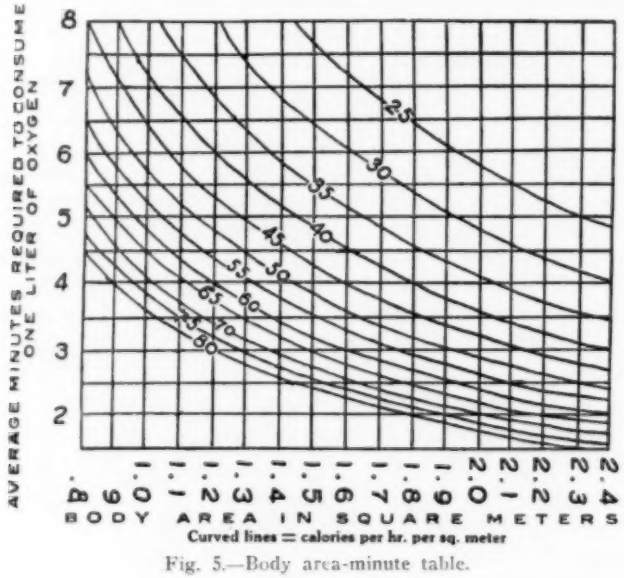

Fig. 5.—Body area-minute table.

or repair. By actual trial the accuracy of the measurement is about ± 2 c.c. out of 1,000 c.c., or 0.2 per cent. error. This degree of accuracy is possible, however, only if the operator is careful each time when reading the pressure to tap on the side of the gage with the tip of the finger, to make sure that the indicator has not encountered some slight resistance in its cog mechanism.

(b) Effect of Oxygen Rich Air on Rate of Oxygen Absorption: Benedict and Higgins[8] have shown that the breathing of oxygen rich air, even up to 90 per cent. oxygen, has no effect on the rate of oxygen absorption. The concentration of oxygen in the

8. Benedict and Higgins: Am. J. Physiol. **28**:1, 1911.

test as described here is never above about 80 per cent. at the beginning, and never below 20 per cent. at the end of the test.

(c) Effect of Temperature: The effect of temperature on the volume of gas contained in the alkali tower is very slight. The rise in temperature averages only 2 C. and the volume of the contained air is only about from 500 to 700 c.c. Error from this source is negligible.

(d) The Nose Clamp: Special caution is necessary in adjusting the nose clamp. If too tight, the patient is in considerable distress in a few moments; if too loose enormous errors will result, since the air of expiration is forced out through small leaks very rapidly. The patient should use only moderate pressure, however, in testing for such leaks. To guard against this source of error, consistent care in adjusting the nose clamp is absolutely essential, regardless of the type of nose clamp employed.

TABLE 2.—Variations in End-Points in Successive Tests on the Same Individual, Without Disconnecting the Subject from the Apparatus *

Test	Stop-watch	Minutes	Percentage Variation from Average
1	4.71	4.71	+0.4
2	9.34	4.63	−1.3
3	14.01	4.67	−0.4
4	18.76	4.75	+1.3
5	23.42	4.66	−0.4
6	28.04	4.62	−1.5
7	32.72	4.68	−0.2
8	37.46	4.74	+1.1
9	42.15	4.69	0.0
10	46.90	4.75	+1.3

* The patient from whom these data were obtained was in coma, showing that knowledge of the test or cooperation on the part of the patient is not essential to accuracy.

(e) The End Point of the Test: The volume of gas in the bag is reduced at the rate of about 15 c.c. per respiration. The bag, therefore, approaches the empty condition gradually. Moreover, the point in the cycle of respiration which gives us the beginning and end-point, namely, the end of expiration, is also constant regardless of the rate and amplitude of respiration, since this point in the cycle represents the position of passivity of the respiratory organs.

The percentage variation in the time required by the patient to consume each successive liter is usually within ± 2 per cent. of the average of the total time, as seen in Table 2. In patients suffering from severe degrees of thyreotoxicosis who are invariably more or less intractable and restless, it is, therefore, of greater importance, clinically, to make two separate duplicate one liter tests, than a single test of two or more liters in succession. In this way the method is rendered practically free from chance errors due to the operator's technical routine.

COMPUTING THE TOTAL CALORIC REQUIREMENTS OF THE PATIENT

When the total caloric loss of an individual under basal metabolism conditions is determined (Fig. 6) for the twenty-four hour period, this does not mean that this caloric equivalent in food will keep him in caloric equilibrium, even with complete rest in bed. A subject with a caloric output of 1,600 calories for twenty-four hours will require about 400 calories in addition to offset the caloric waste caused by the specific dynamic action of the food. This additional amount of food will depend on the proportion of the various food elements since these vary, as stated before, in their effect in stimulating the

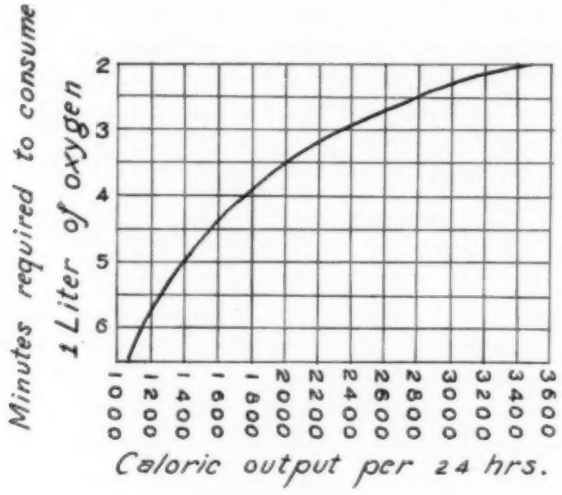

Figure 6.

metabolism above its basal rate. Ordinarily, their combined effect amounts to a waste of between from 20 to 25 per cent. of the total caloric intake. If the subject is not at rest in bed, a still further addition in the caloric intake must, of course, be allowed, the amount depending on the amount of work done by the subject. This is of importance in connection with the regulation of the diet of patients who are abnormally low or high in body weight.

COMPARATIVE TESTS

In comparing the results of tests made by this apparatus with those obtained by the Benedict apparatus, the two instruments agree within very narrow limits. Strict agreement in the reading of the gas volumes could not be expected since the oxygen volume as measured by

the Benedict method is made over water and no allowance made for aqueous tension. This, at 23 C., introduces an error of 3 per cent. in the reading by the Benedict apparatus, and at higher temperatures the error would be disproportionately greater. When correction is made for this factor, the liter of gas, as measured in the apparatus described here, when discharged into the spirometer in the Benedict apparatus showed a rise of the spirometer corresponding very closely to one liter as measured in the latter. With successive tests the agreement was extremely close, ± 3 or 4 c.c. when the same end of the spirometer was used. Three different models of the Benedict apparatus were used in this comparative test with equally close results.

TABLE 3.—Basal Rate in Calories Per Square Meter Per Hour *

Subject	Age	Sex	Rate
S. T.	25	F	36.5
Wy.	26	F	37.0
J. J. T.	32	M	39.6
L. P. G.	24	M	39.2
F. G.	22	F	37.5
M. W.	16	F	41.0
S. P.	13	M	44.0

* These results should be compared with the values given in the table by Aub and DuBois (Charts 1 and 2).

TABLE 4.—Percentage Rise Above Basal Rate *

Patient	Age	Sex	Rise, per Cent.
C. C. H.	35	M	+112
H. P.	47	F	+ 87
P. P.	28	F	+ 51
F. C.	28	M	+ 35
W. S.	52	F	+ 63
A. H.	44	F	+ 26
M. P.	38	F	+ 22

* The rates given in this table are those of persons suffering from hyperthyroidism of varying degrees of severity. All of them had been diagnosed as such by Dr. Charles S. Williamson before being tested. The results show the same ranges of variation reported by others on many cases of this disease.

TABLE 5.—Percentage Rates of Metabolism with Benedict and Jones Apparatus

	Benedict	Jones
Miss G. H.	104-107	103-101
Miss S. F.	157-160	158-150
Mr. N. A.	99-102	98-99
Miss E. P.	122-120	120-121
Mr. H. L.	103-105	104-107

In comparing the percentage rates of metabolism of normal persons, and also hyperthyroid subjects showing varying grades of severity, the values shown in Table 5 represent the usual degree of agreement of the two instruments, when the particular instrument in use is protected against leaks, and when the carbon dioxid absorbing reagent is working properly.

The conclusion is, therefore, justified that either apparatus is quite satisfactory for clinical studies in metabolism, the question of differences in the two instruments centering mainly around the proposition of arriving more easily and quickly at the end result with less chance for error when operated by persons of only average skill.

This instrument has also been used for many months in hundreds of tests on normal persons of all ages and both sexes. The results agree (within the limits of physiological variation) with the average values of normal subjects of given age and sex (see table by Aub and DuBois given on a preceding page). As reported in a previous paper,[9] the apparatus is also being used regularly by the author in clinical research and also in the diagnosis of suspected or borderline cases of myxedema and hyperthyroidism. Duplicates of the instrument have been distributed among clinicians and general practitioners in various parts of the country, who are using it for a like purpose. So far no inherent inaccuracies or technical difficulties have been reported from these sources.

SUMMARY

An apparatus for measuring the rate of oxygen consumption, designed to be portable in a practical sense, is described and illustrated.

Sources of error are discussed and their percentages reduced to a minimum consistent with simplicity.

Mathematical procedures necessary for calculation of the rate of metabolism (from the respiratory quotient, the body area, and the rate of oxygen consumption) are eliminated from the test. The reading is made directly, in terms of calories per hour per square meter of body area.

Independent and comparative tests show its technical variations to be within physiologic and individual variations, and, therefore, adequate to the needs of the clinician as an instrument for measuring basal metabolism.

9. Jones, H. M.: J. A. M. A. **75**:538 (Aug. 21) 1920.

SPIROCHETAL PULMONARY GANGRENE*

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Ever since Obermeier, in 1873, reported the presence of microorganisms of the genus spirocheta, or spirilla, in the blood of patients with relapsing fever, many diseases have been found to be caused by varieties of this species. The most important disease due to spirochetal infection is, of course, syphilis, to which etiologic relationship of the *Spirochaeta pallida* was demonstrated by Schaudinn and Hoffman in 1905. Castellani subsequently found that frambesia tropica, or yaws, was caused by the *Spirochaeta pertenuis*. The etiologic relationship of spirochetes to Vincent's angina, Weil's disease, rat bite fever and pyorrhea alveolaris has likewise been demonstrated.

It is, however, not so well known that certain pathologic processes in the bronchi and lungs are due to the activity of these microorganisms. Many years ago, Eichhorst stated that he found spirochetes in the sputum of some patients suffering from bronchitis. Bertarelli and Volpino observed *Spirochaeta buccalis* and *Spirochaeta pallida* in the sputum of patients affected with heart disease. These observations were not confirmed until Aldo Castellani [1] reported two cases of hemorrhagic bronchitis presenting symptoms simulating those of pulmonary tuberculosis, but no tubercle bacilli could be discovered in the sputum either microscopically or by animal inoculation. In these cases large numbers of spirochetes were found in the sputum. Although Castellani pointed out that similar organisms were also found in the saliva and the superficial scrapings of the gums of his patients, he was inclined to ascribe an etiologic relationship of the spirochetes to the pulmonary disease.

From a study of his cases Castellani arrived at the conclusion that, at least in Ceylon, there is a form of bronchial and pulmonary disease caused by spirochetes. To this disease he gave the name of bronchial spirochetosis.

These findings attracted attention and soon many other observers reported similar cases seen in the tropical world. Jackson, Phalen and Kilbourne [2] and Weston R. Chamberlain [3] reported cases from the

* From the Montefiore Home and Hospital.

1. Castellani, A.: Note on a Peculiar Form of Hemoptysis with Presence of Numerous Spirochetes in the Expectoration, Lancet **1**:1384, 1906.

2. Phalen and Kilbourne: Report of the U. S. Army Board for the Study of Tropical Diseases made to the Surgeon-General, U. S. Army, Washington, D. C., June 30, 1909.

3. Chamberlain: The Occurrence in the Philippines of Associated Spirochetes and Fusiform Bacilli in Ulcers of the Throat (Vincent's Angina), of the Mouth and of the Skin, and in Lesions of the Lungs (Bronchial Spirochetosis), Philippine J. Sc. **6**:489, 1911.

Philippine Islands. J. A. Taylor [4] observed several cases of "pneumonia" among the natives of Uganda in which the causative organisms appeared to be spirochetes. He also mentions one case occurring in a European living in Uganda. J. W. Scott Macfie [5] reported cases observed at Accura, Gold Coast Colony, West Africa, and Frank S. Harper [6] noted the condition of a cook living in Tomall, Northern Territories, Gold Coast, West Africa.

That the disease is not confined to tropical countries was made apparent when Ignatz Feldmann [7] and K. Buday [8] reported several cases observed in Hungary. Buday reported many cases of pulmonary gangrene in which a careful macroscopic and microscopic study was made. The spirochetes and fusiform bacilli were found in large numbers in the gangrenous pulmonary lesions.

During the Word War many causes of bronchial and pulmonary spirochetes were observed among the tropical troops brought to Western Europe. Likewise, in Europeans who had never been in the tropics, spirochetes were found in the sputum in certain cases of bronchitis and pneumonia, and of patients showing symptoms not unlike those of pulmonary tuberculosis. Thus, cases of spirochetosis bronchialis, hemorrhagic spirochetosis, etc., have been reported by G. Delamore,[9] Dalimier,[10] J. A. Thomson,[11] S. Fischera,[12] H. Violle,[13] F. Barbary,[14] P. Nolf,[15] P. Spehl,[16] and many others in France, Italy, England, Belgium, etc. G. A. Lurie,[17] of Chicago, reported a case observed in a Greek lady residing in Uskub, Serbia. One of us observed in the A. E. F. Hospital Center, Bazoilles, Vosges, France, two cases in Americans (white) not unlike those reported by the authors mentioned. Smears from the gangrenous pulmonary areas made at necropsy showed innumerable mouth organisms, including spirochetes. One of

4. Taylor: Bronchal Spirochetosis in Uganda, with Pneumonic Symptoms, Ann. Trop. M. & Hyg. **8**:13, 1914.

5. Macfie: Bronchial Spirochetosis, J. Trop. M. & Hyg. **18**:63, 1915.

6. Harper: Bronchial Spirochetosis, J. Trop. M. & Hyg. **17**:194, 1914.

7. Feldmann: Beitrag zu den durch Bacillus fusiformis und Spirillum dentium herforgerufenen Infektionen mit besonderer Berücksichtigung der Eiterungen, Wiener. klin. Wchnschr. **19**:695, 1906.

8. Buday: Histologische Untersuchungen über die Entstehungsweise der Lungengangrän, Beitr. z. path. Anat. u. z. allg. Path. **48**:700, 1910.

9. Delamore: Bull. et mem. Soc. méd: d. hôp. de Par. **43**:526, 1919.

10. Dalimier: Presse méd. **27**:124, 1919.

11. Thomson: Pulmonary Spirochetosis, Brit. M. J. **2**:775, 1919.

12. Fischera: Riforma med. **34**:384, 1918.

13. Violle: Bull. de l'Acad. de méd., Par. **79**:429, 1918.

14. Barbary: Bull. de l'Acad de méd., Par. **79**:461, 1918.

15. Nolf and Spehl: Arch. méd. Belges **71**:1, 1918.

16. Nolf, P.: Fetid Spirillar Bronchitis and Pulmonary Gangrene, Arch. Int. Med. **25**:429 (April) 1920.

17. Lurie, G. A.: Note on Castellani's Broncho-Spirochetosis, J. Trop. Med. & Hyg. **18**:269, 1915.

these patients had marked dental caries, and smears from the material in the cavities likewise showed many mouth organisms including spirochetes.

It is noteworthy that even before these reports were made, J. H. Rothwell [18] reported two cases of "bronchial Vincent's angina" with symptoms and signs simulating pneumonia, but in which the sputum was found to be full of spirillae and fusiform bacilli.

More recently Ralph R. Mellon [19] reported a series of cases of whooping cough, pneumonia and empyema from Rochester, N. Y., in

Fig. 1.—Right lung: Extensive bronchopneumonia with gangrenous ulceration in right lower lobe.

which fusiform bacilli were discovered in the sputum. A. N. Sinclair [20] also found in the Philippine Islands numerous cases of pulmonary hemorrhage of tuberculous origin, in which Vincent's spirochetes, or fusiform bacilli were discovered in the sputum. It is his opinion that the presence of fusiform bacilli predisposes to hemoptysis

18. Rothwell: Bronchial Vincent's Angina, J. A. M. A. **54**:1867 (June 4) 1910.

19. Mellon: A Clinical and Bacteriological Study of Fusiform Bacillus Infection, New York State J. M. **20**:187, 1920.

20. Sinclair: Vincent's Spirochetae and Hemorrhage in Pulmonary Tuberculosis, Am. Rev. Tuberc. **4**:201, 1920.

in tuberculous individuals, and that hemorrhage only rarely occurs in incipient cases unless they are present.

The following case of pneumonia with gangrenous ulceration, apparently caused by spirochetes, observed at the Montefiore Hospital, is believed to be the first reported in New York:

REPORT OF CASE

M. S. (No. 027757), aged 33, native of Russia, six years in the United States; tailor; admitted April 19, 1920, as a case of pulmonary tuberculosis.

Symptoms on admission: Fever, reaching 105 F., of a continuous type; severe, incessant cough, copious expectoration of foul smelling, greenish mate-

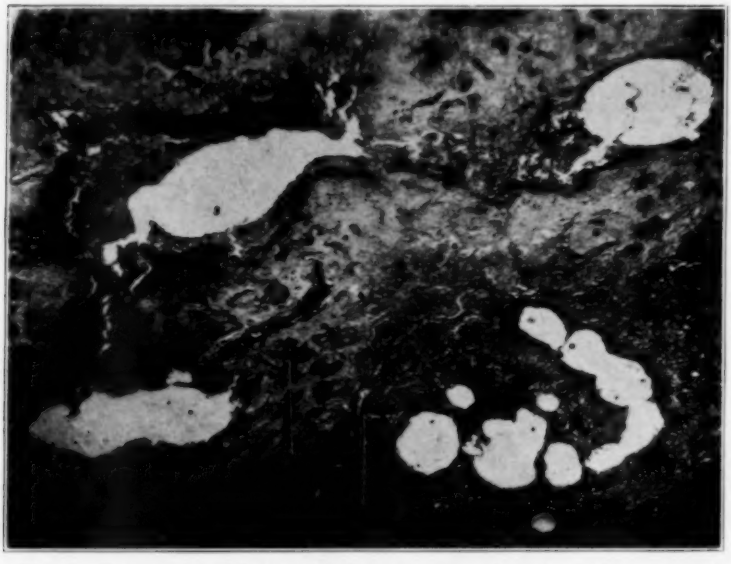

Fig. 2.—Pneumonia with associated gangrenous ulceration. Low power.

rial, at times bloody; dyspnea, cyanosis, prostration. The mental state of the patient precluded obtaining a clear cut and reliable history of the case, but combining the data elicited from him with those given by his friends who visited him at the hospital, we find that his family and personal past history present no conditions which may have had any bearing on his present state. He had been married for eight years, had two children, both alive and well, and had worked at his trade, tailoring, without interruption due to illness, till March 15, 1919, when he began to cough and expectorate. This cough, however, was at the beginning so slight, that he believed it to be due to excessive smoking and he paid little attention to it.

During the first week of April, he was suddenly seized with vomiting, followed by fever and prostration. A physician who examined him at that time informed him that "weak lungs" were responsible for his trouble and advised a trip to the mountains. The severity of the disease prevented his leaving the city. The frequent chills, high fever and sweats became very marked and

he was referred to the Montefiore Hospital with a diagnosis of acute progressive pulmonary tuberculosis.

On admission it was felt that we were dealing with a case of gangrene of the lungs. The foul, sharp, penetrating odor of the breath and expectoration pointed in this direction; the high fever, the sweats and the prostration gave support to this provisional diagnosis. Physical exploration of the chest revealed a suspended area of flatness in the middle of the right side of the chest; this flatness was most marked over the lower two-thirds of the interscapular space. On auscultation the breath sounds were found feeble, hardly audible over the flat area, while over the upper lobe of the right lung, medium sized, moist râles were heard; over the right base, in the axillary space, a soft friction sound was made out. There were also signs of fluid in the left pleural cavity, flatness, feeble breath sounds, abolition of vocal fremitus, dulness

Fig. 3.—Smear from gums (Fontana stain), high power. Spirochetes and other organisms.

in Traube's space, etc. These signs elicited on physical examination of the chest suggested either an interlobar empyema which had broken through a bronchus, a pulmonary abscess which may thus have originated, or gangrene of the right lung. A roentgenogram confirmed the findings of physical exploration. A large, somewhat round, shadow, occupying the middle third of the right lung, was disclosed. The rest of the lung showed evidences of hyperaeration.

Of the laboratory findings, the following are of interest: Blood—hemoglobin, 70 per cent.; leukocytes, 21,000; lymphocytes, 18 per cent.; polymorphonuclears, 80 per cent. Wassermann reaction (blood) negative; urea N = 13.7 per 100 c.c.; creatinin, 4.3 per 100 c.c. Urine: acid; sp. gr. 1.022; slight amount of indican; no albumin; no sugar;

Ehrlich's diazo reaction negative; no casts; no tubercle bacilli. Repeated search also failed to disclose tubercle bacilli in the sputum.

Correlating the history with the physical and roentgenographic signs it appeared that the process was not an interlobar empyema. There was no history of an acute onset with pain in the chest, fever, etc., nor has the temperature declined sufficiently to indicate that empyema broke through a bronchus and was being drained. The fetid odor of the expectoration also spoke against an interlobar abscess; there was no history of an acute pulmonary disease such as pneumonia, preceding it. As soon as the patient began to expectorate, the sputum

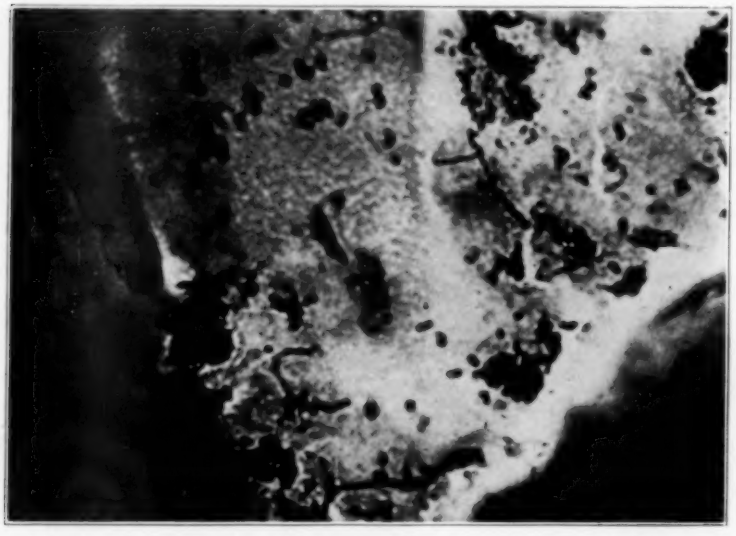

Fig. 4.—Gangrenous lung (Fontana stain), high power. Spirochetes and other organisms.

had the sharp penetrating odor characteristic of gangrene. A foreign body in a bronchus was thought of, but the history, symptomatology and the roentgenogram spoke against it.

The history, symptomatology, physical and roentgenographic signs, combined with the laboratory findings, were thus all against a diagnosis of tuberculosis. As has already been stated, an interlobar empyema was also excluded. The slow onset, the absence of a history of acute pulmonary disease, or operation on the tonsils, etc., also spoke against pulmonary abscess. Furthermore, the expectorated material had the intensely penetrating odor characteristic of gangrene of the lung.

The sputum was then again sent to the laboratory with a request that a careful search be made for spirochetes. With the Fontana

stain, the presence of fusiform bacilli and spirochetes was readily demonstrated. Inasmuch as these organisms are very often found on the gums of healthy individuals, and especially the gums of those who suffer from pyorrhea alveolaris, the sputum was carefully washed, and it was found to contain numerous spirochetes. The material scraped from the gums was then examined and many spirochetes, of the morphology of *Spirocheta microdentium* and *S. macrodentium* were found; some had the morphology of the *Spirochaeta bronchialis* of Castellani. A few had an appearance not unlike that of *Spirochaeta pallida*.

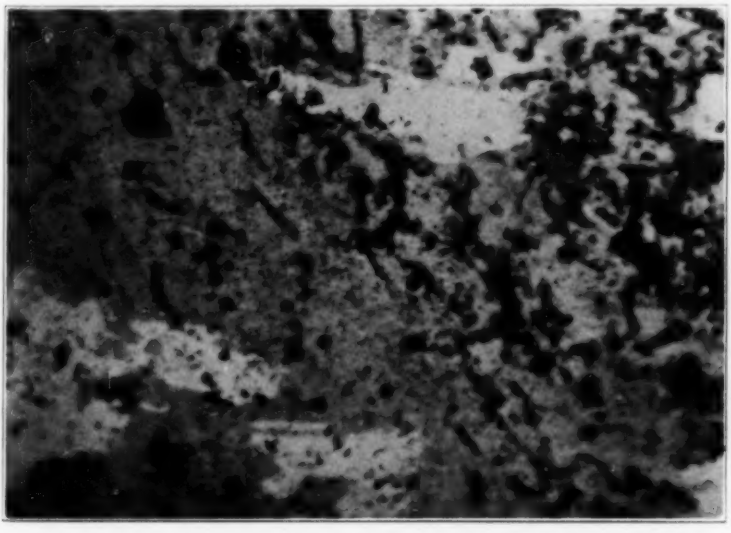

Fig. 5.—Smear from gangrenous lung (Fontana stain), high power. Spirochetes and other organisms.

The usual symptomatic treatment apparently had no effect on the progress of the disease. The fever remained high, between 103 and 104 F.; cerebral symptoms made their appearance and the prostration remained severe. The foul odor of the expectoration and the weakness of the patient increased. Reports have shown that in some cases of abscess and gangrene of the lung, artificial pneumothorax has proven of value, though in the experience of one of us, it has never been a success in this class of cases. On entering the right pleural cavity with the pneumothorax needle May 5 we found excellent negative pressure with respiratory oscillations and allowed 400 c.c. of air to enter. The intrapleural pressure remained minus 10 after the initial inflation.

No improvement was noted in the general condition of the patient after the pneumothorax was induced. The fever remained high, the prostration continued, and the weakness increased. May 6, the cerebral symptoms became accentuated, the patient died at 4:30, manifesting intense dyspnea and cyanosis.

For special reasons a complete necropsy could not be made; only the thoracic and abdominal viscera were removed for examination.

The lungs showed extensive coalescing lobular and bronchopneumonia of both upper lobes and the right middle lobe. In the right lower lobe, associated with the consolidated lung, there was extensive gangrenous ulceration, the ulcerated areas varying in size from several millimeters to a cavity 4 cm. in diameter.

Microscopically, the picture was that of extensive lobular and bronchopneumonic exudation with numerous areas of necrosis and gangrene. With Fontana and MacCallum stains, spirochetes and fusiform bacilli were observed in large numbers in the necrotic and gangrenous areas. The following is an abstract of the necropsy protocol:

NECROPSY PROTOCOL

The larynx and upper part of the trachea were not removed. The lower portion of the trachea and right bronchus show an intensely injected, swollen mucosa. In the lumen, there is a considerable amount of mucopurulent material. In the left pleural sac, several hundred c.c. of thin, blood tinged fluid were found.

Lungs: All lobes much more voluminous than usual. The upper lobes cushiony, soggy; middle and lower lobes soggy, solid. The pleura is thickened over the upper lobes and over the posterior portions of the lower lobes. There are sheetlike, fibrous tags in these areas. There is some fibrinous exudate over the lateral and median portions of both lower lobes. Glands at the hilum enlarged, pulpy, edematous, injected, pigmented. On section of the upper lobes, a moist, dark red surface presents. The tissue is apparently congested and edematous. There is no definite consolidation. There is a considerable amount of thin fluid in the air sacs. The bronchial branches show an injected, swollen mucosa, overlaid by blood tinged, mucopurulent material. Right middle lobe on section, shows extensive consolidation, the patches small, several millimeters to one centimeter in diameter, almost adjoining one another throughout the lobe. These areas are soft, yellowish, almost purulent. They are, however, considerably more coherent than abscesses. Both lower lobes on section show extensive, patchy consolidation, the patches almost adjoining each other throughout the lobes. This is especially true in the posterior portions. The patches in these lobes also vary in size from several millimeters to one centimeter. They vary in color from reddish yellow to dark green. The latter color is especially marked in the right lower lobe. In addition, many of the dark green, consolidated patches show central ulceration. The cavities vary in size from a few millimeters to four centimeters in diameter. The large cavity is present in the upper anterior portion of the right lower lobe, well below and median to the apical portion. There is no sharp reaction zone about the cavities. They are all surrounded by greenish, consolidated lung. Within the cavities, there is thin, greenish, necrotic material. The ulceration in the left lower lobe is much less advanced than in the right lower. The bronchial tree throughout, shows beginning calcification of the cartilages. The mucosa is swollen, injected, overlaid by mucopurulent material. In places, espe-

cially in the right lower lobe, the mucosa has a greenish tint. The lungs have an intense, penetrating, disagreeable odor.

Smears from the yellow and green consolidated areas and cavities show innumerable, gram-negative spirillae and spirochetes resembling *Spirochaeta microdentium, S. macrodentium* and *S. refringens,* the latter present in small numbers. Throughout the smears there are also innumerable gram-negative bacilli. Some of these are small, resembling *Bacillus influenzae;* others are larger. Some of the larger gram-negative bacilli have a safety-pin appearance, resembling colon bacilli. In addition, there are a large number of rounded, gram-negative cocci and some diplococci. In the smears the following gram-positive organisms were noted: innumerable diphtheroids, many rounded cocci, rounded and lancet shaped diplococci, scattered small chains of rounded cocci, also scattered, straight and curved, beaded bacilli with tapering ends about the size of gas bacilli and somewhat smaller.

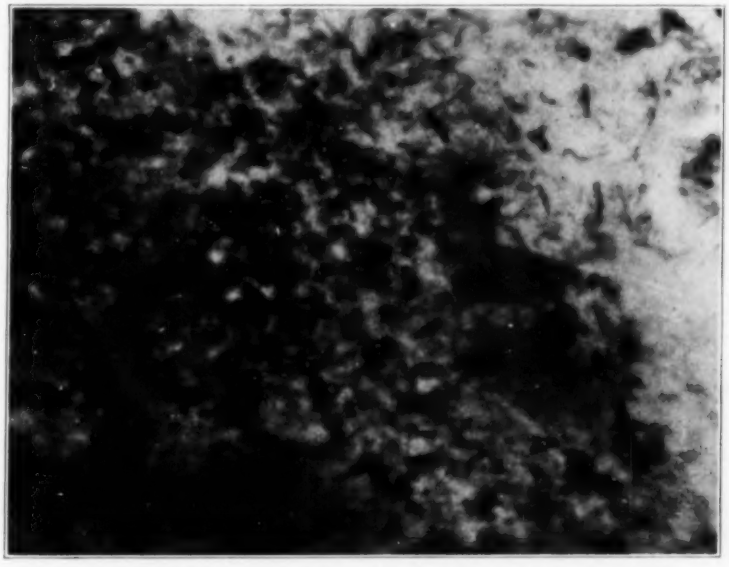

Fig. 6.—Section of gangrenous lung (MacCallum stain), high power. Fusiform bacilli and other organisms.

Microscopic Sections: Section 1 shows on gross inspection a number of circumscribed areas from one to several millimeters in diameter with pink periphery and bluish center. Alveoli in general apparently filled. Under low power, the circumscribed areas mentioned above are seen to be composed of a zone of necrotic pink stained lung tissue and exudate, the central portions bluish, consisting of masses of organisms. There are many of these necrotic areas in the section; in places they adjoin one another; in places they are discrete and vary in size from that of a glomerulus to several millimeters in diameter. In addition to these areas, the alveoli throughout the section in general are filled with exudate composed of swollen alveolar cells and amorphous pink stained material and a few wandering cells. The alveolar walls, in general, show swollen epithelial cells with blood vessels moderately engorged. In places, the alveoli are filled in great part by red blood cells. Portions of the pleura in the section are swollen, distended by amorphous

pink stained material, red blood cells and scattered wandering cells. There is a small amount of fibrin present. In places there is definite beginning organization of the exudate.

Section 4 shows in addition to circumscribed necrotic areas with masses of blue stained organisms, the adjoining alveoli filled with pus cells and mononuclear cells, the nuclei of the majority of these being deeply stained (pyknotic). External to the alveoli filled with pus cells, are alveoli filled with large mononuclear cells, some containing blood pigment, some pus cells, some red blood cells and some amorphous pink stained material. The pulmonary vessels throughout are engorged. In this section there are numerous groups of alveoli filled with exudate rich in polymorphonuclears; in places there is definite necrosis of the exudate. In places there are circumscribed masses of blue stained organisms. There are scattered bronchial branches filled with necrotic exudate containing blue stained organisms, the epithelium of these bronchial branches is almost homogenously pink stained, the nuclei being barely visible. Throughout all coats of bronchial branches the blood vessels are engorged. There is apparently considerable thickening due to the presence of granulation tissue. In places, in the section the alveoli contain in great part amorphous pink stained material (serum) and scattered, desquamated cells. In places, the exudate is present in the peribronchial alveoli, in places the exudate is apparently lobular in distribution and varies in proportion of serum, large phagocytic mononuclear cells, pus cells and red blood cells. In places, there is definite organization of the exudate; in other places there is necrosis and ulceration associated with blue stained masses of organisms.

Section 5 shows a wall of a large cavity composed of amorphous pink stained necrotic material in the innermost zone, external to which there is granulation tissue composed of numerous engorged capillaries and fairly densely layered connective tissue cells. In places, the connective tissue cells are loosely connected. In places, there are numerous plasma cells in the granulation tissue. External to this zone there are numerous, somewhat collapsed alveoli filled with exudate, varying in character, as described above. In this section also there are fair sized bronchial branches with greatly thickened walls, due to granulation tissue.

Sections of the lung stained by Fontana method show in the necrotic areas a considerable number of spirochetes resembling *Spirochaeta macrodentium* and *S. microdentium*. With this stain, innumerable other organisms are observed in the necrotic and consolidated portions. Sections stained by MacCallum's stain show in the consolidated and necrotic areas innumerable gram-positive organisms including gram-positive bacilli, some of these having the morphology of diphtheroids; gram-negative bacilli, some having the morphology of influenza bacilli, also gram-positive and gram-negative cocci. There are also many large slightly curved gram-positive bacilli, not unlike the fusiform bacilli of Vincent's angina. The spirochetes are poorly stained by this method. With this stain the predominant organism is the somewhat gram-positive bacillus.

DISCUSSION

The presence of numerous spirochetes in the gangrenous portions of the lung in the case reported, suggests their etiologic relationship to the lesion. It is probable that the spirochetes responsible for the gangrene in this case are of the type Castellani calls *Spirochaeta bronchialis*. While, of course, there are present in the lesions numerous mouth organisms, the overwhelming number of the spirochetes, as well as the study of their location in the diseased area, and the cellular reaction to their presence, compels the conclusion that the predominantly gangrenous lesions are to be directly attributed to the spirochetes.

THE SIGNIFICANCE OF THE ACIDOSIS OF METHYL ALCOHOL POISONING *

CHARLES C. HASKELL, S. P. HILEMAN AND W. R. GARDNER
RICHMOND, VA.

The increase in the number of cases of poisoning by methyl alcohol that has occurred recently renders particularly interesting the report of the favorable results obtained by Harrop and Benedict [1] in the treatment of a case of such poisoning with sodium bicarbonate. The rationale of this treatment depends on the fact first demonstrated by Król [2] that there is an abnormal excretion of acid bodies in the urine following the ingestion of methyl alcohol. Since Pohl [3] had previously shown that methyl alcohol is slowly and incompletely oxidized in the body, a considerable proportion of that administered being excreted in the shape of formic acid, it was believed that this formic acid was responsible for the "acidosis." Król, however, found that the formic acid accounted for only a small part of the ammonia of the urine, indicating that other organic acids were excreted in abnormal amounts. Tyson and Schoenberg [4] also found that there was an acidosis, as determined by the decreased titratable alkalinity of the body fluids, when methyl alcohol was administered by inhalation. While the suggestion has been made that the acidosis might be an important factor in producing the poisonous action of methyl alcohol, apparently Harrop and Benedict were the first to treat a patient on this assumption. In the case reported by these authors there was a definite reduction in the reserve alkali and there was also the characteristic air hunger.

It is now known that a reduction of the reserve alkali of the blood occurs in a variety of pathologic states, but the exact significance of this reduction is not clearly understood. There is evidence that strongly suggests that the disturbance of the acid-base balance may, in itself, cause definite anatomic changes. Thus, Graham,[5] studying delayed

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* From the laboratory of pharmacology, Medical College of Virginia.

1. Harrop and Benedict: Acute Methyl Alcohol Poisoning Associated with Acidosis, J. A. M. A. **74**:25 (Jan. 3) 1920.

2. Król: Cited by Harrop and Benedict.[1]

3. Pohl: Ueber die Oxydation des Methyl- und Aethylalkahols im Thierkörper, Arch. f. exper. Path. u. Pharmakol. **31**:281, 1892.

4. Tyson and Schoenberg: Experimental Researches in Methyl Alcohol Inhalation, J. A. M. A. **63**:915 (Sept. 12) 1914.

5. Graham: Late Poisoning with Chloroform and Other Alkyl Halides in Relationship to the Halogen Acids Formed by Their Chemical Dissociation, J. Exper. M. **22**:48, 1915; Sodium Carbonate in Chloroform Poisoning. Arch. Int. Med. **25**:575 (May) 1920.

chloroform poisoning, finds that sodium carbonate administration protects against the lesions seen in the liver, and from this and other considerations, he believes that the lesions are caused by the production of hydrochloric acid from a splitting of the chloroform in the body. MacNider [6] in a similar manner finds that the carbonate lessens or prevents the kidney injury that is seen following the administration of uranium nitrate to dogs, and suggests the possibility that these renal injuries are due to the formation of acids as a result of a depressant action the uranium exerts on oxidative processes in the cell. The discovery of a reduction of the alkali reserve in the patient under their care is probably justification for the institution of alkali therapy by Harrop and Benedict, and the results are sufficiently striking to give encouragement. However, one case is far from conclusive, so it was deemed advisable to endeavor to ascertain by animal experimentation the importance of the rôle of acidosis in the production of the symptoms of methyl alcohol poisoning and the benefits to be derived by the administration of sodium bicarbonate.

As was pointed out by Joffroy and Serveaux,[7] Pohl,[8] Hunt [8] and others, poisoning by wood alcohol may be of either the chronic or acute type. Owing to the incomplete oxidation and slow excretion of this alcohol, there is a decided tendency to cumulation, so that small, nontoxic doses given repeatedly will lead eventually to severe or fatal poisoning. This type of case presents a hopeless outlook from the beginning, because the damage has already been done before the patient comes under observation. On the other hand, where poisoning has followed the ingestion of a single large dose or of a few repeated large doses, it is probable that the outcome may be influenced by treatment, for here the attempt may be made to neutralize the toxic agent or hasten its elimination before irreparable damage has been done. Many of the recent cases were of this second type, Harrop and Benedict's being illustrative. Therefore, we have made the attempt to determine the acute toxicity of methyl alcohol for dogs; to ascertain whether an acidosis occurs in animals so poisoned, and to estimate the value of alkaline treatment under such conditions.

According to Hunt,[8] the toxicity of the purest available methyl alcohol is closely approximated by that of ordinary "Columbian spirits" and similar commercial preparations. Nevertheless, we have used a

6. MacNider: The Inhibition of the Toxicity of Uranium Nitrate by Sodium Carbonate, and the Protection of the Kidney Acutely Nephropathic from Uranium from the Toxic Action of an Anesthetic by Sodium Carbonate. J. Exper. M. **23**:171, 1916.

7. Joffroy and Serveaux: Mensuration de la toxicite experimentale et de la toxicite vraie de l'alcool methylique. Arch. de méd. exper. **8**:473, 1896.

8. Hunt: The Toxicity of Methyl Alcohol. Bull. Johns Hopkins Hosp. **13**:213, 1902.

high grade of methyl alcohol, marketed by Merck under the title of Reagent Alcohol Methylic, and, according to the label on the bottles, having the following maximum limit of foreign substances: Non-volatile matter, 0.0020 per cent.; acetone, 0.0150 per cent.; ethyl alcohol, 1.0000 per cent.; empyreumatic substances, 0.0000 per cent.; aldehyds, 0.0000 per cent.; substances oxidizable by permanganate, 0.0000 per cent.; chloroform, 0.0100 per cent.

Dogs were used as experimental animals, the drug being given undiluted either subcutaneously or orally. The injections were made at room temperature from a buret connected with a hypodermic needle for the subcutaneous injections or with a catheter used as a stomach tube when oral administration was practiced. In the latter case, the dogs received a preliminary injection of 10 mg. morphin sulphate per kilogram of body weight in order to prevent emesis from the irritant action of the alcohol in the stomach.

To detect the existence of an acidosis, the method of Van Slyke and Cullen for determining the carbon dioxid combining power of the plasma was used.[9] Blood was generally drawn from the external jugular vein; occasionally from the femoral; and, in one instance, from the heart. It was found convenient to employ a 10 c.c. syringe, coated with petrolatum. On securing approximately 10 c.c. of blood, the needle was removed and the syringe connected with a short piece of oiled rubber tubing, through which the blood was forced into a centrifuge tube, containing a small amount of liquid petrolatum and a few drops of a saturated solution of potassium oxalate. By means of the tube, blood and oxalate were well mixed. We could not detect that these slight modifications exerted any influence on the values obtained, and clotting was less likely to occur.

With sufficiently large doses of the alcohol, the usual intoxication was produced with its slow onset and persistent coma. Twitching of the facial muscles invariably occurred, but we did not observe actual convulsions from any dose of the alcohol. The subcutaneous injection of the strong alcohol caused some slight temporary discomfort, but this soon passed off. Following either method of administration, after the onset of the coma, many of the dogs cried out constantly, their cries becoming much louder if they were handled in any way.

When alcohol is injected subcutaneously, it is seen that there exists considerable variation in the resistance of different animals to the poisonous action. Thus, one dog died following the injection of 5 c.c. alcohol per kilogram of body weight and one dog died following a dose of 6 c.c. per kilogram of body weight, while two dogs that were

9. Van Slyke and Cullen: The Bicarbonate Concentration of the Blood Plasma, etc., J. Biol. Chem. **30**:289, 1917.

given 7 c.c. alcohol per kilogram of body weight survived. A dose of 8 c.c. was fatal to three dogs. Other investigators have placed the lethal subcutaneous dose for dogs at a slightly higher figure; Dujardin-Beaumetz and Audigé [10] stating it to be about 7 gm. per kilogram, while Joffroy and Serveaux [7] place the lethal intramuscular dose for dogs at about 9 c.c.

Our results are given in Table 1.

TABLE 1.—Results of Subcutaneous Injection of Methyl Alcohol

Number of Experiment	Weight in Kg.	Dose of Alcohol in C.c. per Kg.	Result
1	16.1	4	Survived
1	6.1	5	Died
2	14.1	6	Died
3	9.5	7	Recovered
5-A	12.95	7	Recovered
7	8.18	8	Died
8	5.1	8	Died
9	7.16	8	Died

When the alcohol is given orally, similar individual variations are encountered. Thus, it is found that one dog succumbed to a dose of 5 c.c. per kilogram; two dogs died from a dose of 6 c.c. per kilogram, while two of eight survived a dose of 8 c.c. per kilogram. Therefore, even this last dose cannot be said to be the surely fatal dose, but, at the time these experiments were carried out, the majority of dogs succumbed to it. These results are tabulated in Table 2.

TABLE 2.—Results from Oral Administration of Methyl Alcohol to Dogs

Number of Experiment	Weight of Dog in Kg.	Alcohol, C.c. per Kg.	Result
90	4.66	4	Recovered
19	9.8	4	Recovered
91	3.86	5	Died in less than 140 hours
20	7.3	6	Survived
87	4.96	6	Died in 53 hours
88	6.93	6	Died between 120 and 130 hours
30	17.7	8	Recovered
86	10.08	8	Recovered
39	7.5	8	Died in less than 60 hours
28	3.4	8	Died in less than 48 hours
29	7.0	8	Died in less than 120 hours
89	7.27	8	Died in less than 40 hours
43	12.5	8	Died in less than 72 hours
55	8.18	8	Died in less than 16 hours
23	4.95	8	Died between 48 and 60 hours

In dogs showing severe symptoms of poisoning after either the subcutaneous or oral administration of methly alcohol, there is usually a marked reduction in the plasma bicarbonate carbon dioxid combining power. This is well illustrated by the results obtained with Dogs 1 and

10. Dujardin-Beaumetz and Audige: Cited by Hunt.[8]

2. The alcohol was injected subcutaneously into these two dogs, the doses being 5 and 6 c.c. per kilogram, respectively. Death ensued in both instances. Prior to the injection of the alcohol, the Van Slyke test gave a plasma bicarbonate value of 56 and 58 c.c. of carbon dioxid per 100 c.c. of blood, respectively. Eighteen hours later, these values had fallen to 43 and 45 c.c.; while, at the end of forty-eight hours, the figures were 26 and 24 c.c. On the other hand, Dog 3 received a subcutaneous dose of 7 c.c. of alcohol per kilogram, but failed to develop the severe intoxication seen in the other dogs; in keeping with which, the plasma bicarbonate carbon dioxid did not fall below 33 c.c. per 100 c.c. and soon returned toward normal. This last animal recovered completely without treatment. Figure 1 represents graphically the changes seen in the reserve alkali in these three dogs.

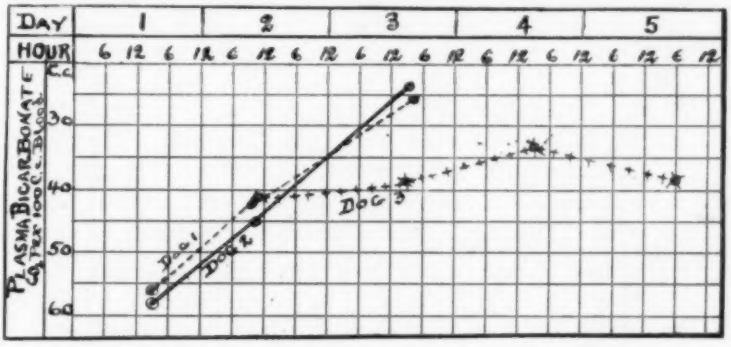

Fig. 1.—Changes in reserve alkali in three dogs following subcutaneous injection of alcohol. Dog 1 received 5 c.c. methyl alcohol per kg., died. Dog 2, 6 c.c. alcohol per kg., died. Dog 3, 7 c.c. alcohol per kg., lived.

In a similar manner, the intensity of the symptoms and the degree of acidosis run parallel in Dogs 90 and 91, to whom oral doses of 4 and 5 c.c. per kilogram, respectively, were given. Dog 90 was not seriously affected, and there was a relatively small reduction in the plasma bicarbonate carbon dioxid. On the other hand, dog 91 was very sick, dying on the fifth day, and her reserve alkali was correspondingly reduced. Figure 2 illustrates the results seen.

Such observations as these give additional support to the view that the acidosis plays an etiologic rôle in the production of the symptoms following poisoning by methyl alcohol and serves as justification for the opinion that alkaline therapy is indicated here. We have obtained evidence, however, which leads us to believe that:

1. In dogs poisoned with methyl alcohol, the severity of the intoxication is, at times, entirely at variance with the degree of acidosis.

2. The intravenous administration of alkali is a procedure by no means devoid of danger.

3. Alkali, in the form of sodium bicarbonate, has, in itself, little or no influence on the course of poisoning.

PROTOCOL OF EXPERIMENTS

The following experiments may be cited in support of the first point.

EXPERIMENT 23.—April 30, 1920. Female poodle, weight, 4.95 kg.
3:34 p. m., received 10 mg. morphin sulphate per kilogram subcutaneously.
4:30 p. m., received 10 c.c. methyl alcohol per kilogram orally.
May 1, 9:30 a. m.: Very deeply unconscious and unresponsive to all ordinary stimuli.
11:49 a. m.: Condition about the same; blood from jugular gives plasma bicarbonate carbon dioxid, 61.3 c.c.
Dog died the night of May 2 without any improvement in symptoms.

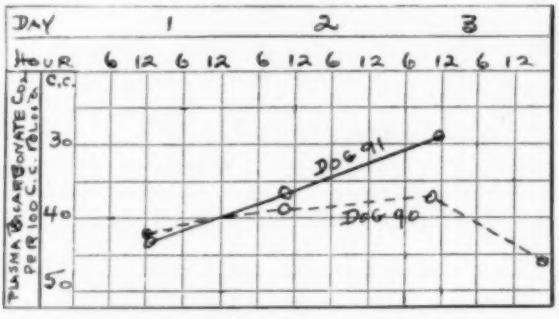

Fig. 2.—Two dogs were given oral doses of methyl alcohol. Dog 90 received 4 c.c. per kg. and lived. Dog 91 received 5 c.c. per kg., and died.

Here is an animal that received a dose of methyl alcohol sufficient to cause evidences of severe intoxication and, eventually, death, yet at the end of nineteen hours, when the depression was profound, there was no reduction in the reserve alkali of the blood. Even more striking, however, is the next experiment.

EXPERIMENT 16.—April 30, 1920. Female fox terrier, weight 4.8 kg.
10:52 a. m., received 10 mg. morphin sulphate per kilogram subcutaneously.
11:25 a m., received 10 c.c. methyl alcohol per kilogram orally.
4:40 p. m.: Deeply unconscious. Blood carbon dioxid, 66.1 c.c.
4:52 p. m.: Respiration ceases; heart beats a few times and then stops.

Twelve minutes before a fatal termination, the plasma bicarbonate carbon dioxid was quite high. The next experiment shows that a reduction of the alkali reserve does not always lead to or accompany severe symptoms.

EXPERIMENT 89.—July 24, 1920. Black female mongrel; weight, 10.8 kg.
11:44 a. m., received 10 mg. morphin sulphate per kilogram subcutaneously.
12:02 p. m.: Blood carbon dioxid, 43.9 c.c.
12:18 p. m., received 8 c.c. methyl alcohol per kilogram orally.
July 25, 10 a. m.: Only after repeated efforts is dog able to rise to her feet, when she staggers around, almost falling. Blood carbon dioxid, 33.2 c.c.
July 28, 9:43 a. m.: Dog practically normal. Eats greedily and runs without the least evidence of unsteadiness. Blood carbon dioxid, 29.6 c.c.
July 31, 9 a. m.: Dog seems fully normal.

July 25, the dog seemed to be severely poisoned, the plasma bicarbonate carbon dioxid, in keeping with this, being reduced almost 25 per cent. Three days later, however, the visible evidences of intoxication had entirely disappeared, in spite of the fact that the plasma bicarbonate carbon dioxid had undergone a still further reduction. It is interesting to chart the results obtained in Experiment 89 and compare them with those obtained in Dog 91. In this dog, there was

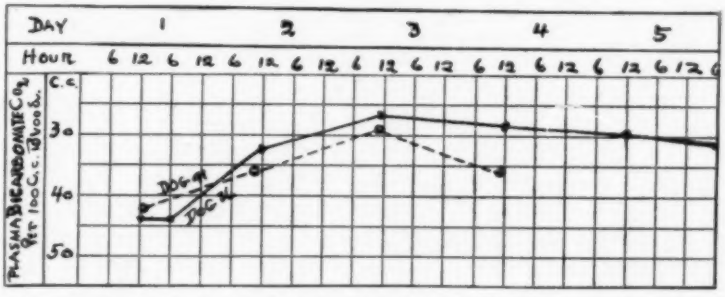

Fig. 3.—Comparison of results in Dogs 91 and 86, who were given 5 and 8 c.c. methyl alcohol, respectively, per kg. Dog 91 died. Dog 86 lived.

a steady increase in the severity of the symptoms, the dog dying on the fifth day, but, accompanying this, there was a rise in the reserve alkali. This comparison is given in Figure 3.

Sodium bicarbonate is the salt generally employed in the treatment of acidosis. While usually given by mouth or rectum, not infrequently it is injected intravenously, especially when there seems to be urgent need or when, as in Harrop and Benedict's case, vomiting occurred after its oral administration. There does not seem to be any definite rule as to the strength of solution to be employed, or as to the amount that may be injected. Harrop and Benedict used a 5 per cent. solution, and in a number of instances in the literature mention is made of the use of a solution of this strength in other conditions than the acidosis of methyl alcohol poisoning. The amount given varies greatly. Not infrequently as much as a liter of a 5 per cent. solution is injected intravenously in adults, but Harrop and Benedict used only 500 c.c.

as their maximum single injection. The weight of their patient is not stated, but, assuming her to have been of average size, this would mean a dose of from 8 to 10 c.c. per kilogram.

In most of our early experiments, a solution of 5 per cent. strength was used. This was made by dissolving the bicarbonate in distilled water or in tap water; boiling the solution for a few minutes, allowing it to cool and then passing carbon dioxid through it for about thirty minutes. Twice, a solution of 10 per cent. strength was used. Using no anesthetic, the vein was not exposed, the injections of the bicarbonate solution being made through the skin into the jugular vein as a rule, occasionally into an ear vein. Naturally, it was of importance to avoid injury to the vessel as much as possible, because the production of a hematoma rendered the vein of no use for subsequent injections. Impressed by this, we attempted to make these earlier injections as rapidly as practicable, using a 19 gage needle and exerting pressure on the fluid in the transfusion flask, so that the total amount was introduced in from three to eight minutes. The results obtained by this method of treatment are given in Table 3.

TABLE 3.—Results of Treatment with 5 and 10 Per Cent. Sodium Bicarbonate Solution; Rapid Injection

Number of Experiment	Weight in Kg.	Dose of Alcohol in C.c. per Kg.	Strength of Solution of Sodium Bicarbonate	Result
5*	14.0	7	5%	Died
10*	17.0	8	10%	Died
11*	21.8	8	10%	Died
12*	23.2	8	5%	Died
27	8.2	8	5%	Died
32	16.6	8	5%	Died
35	6.1	8	5%	Died

* In these dogs, the alcohol was injected subcutaneously; in the others it was given orally.

An experience such as this is not likely to render one enthusiastic over the alkaline treatment, but an analysis of the experiments discloses the probability that death was due in every instance to a toxic action of the bicarbonate and not due to the alcohol. Of the seven dogs, six died immediately after the injection of the solution, and all showed such striking symptoms as a result of this injection, that it is scarcely conceivable that death was due to any other cause. This is well shown in the following experiment.

Experiment 10.—April 26, 1920. Black and white male hound; weight, 17 kg.

5:26 p. m., received 8 c.c. methyl alcohol per kilogram injected subcutaneously.

5:55-5:58 p. m., received 10 c.c. per kg. of a 5 per cent. sodium bicarbonate solution injected into the jugular. No untoward symptoms.

April 27, 10:06 a. m.: Deeply unconscious. Blood carbon dioxid, 62 c.c.

11:50-11:54 a. m.: 5 c.c. per kilogram of a 10 per cent. sodium bicarbonate solution injected into the jugular. No untoward symptoms.

April 28, 11:10 a. m.: Condition about the same. Blood carbon dioxid, 52.6 c.c.

4:12-4:14 p. m.: 4 c.c. per kilogram of a 10 per cent. sodium bicarbonate solution injected into the jugular. Immediate stiffening of limbs and arching of back; respiration deepened and quickened; heart pulsations not palpable; cardiac massage and artificial respiration ineffectual.

Of the remaining six dogs, five died immediately on receiving the sodium bicarbonate injections; one developed convulsions following the injection but breathed spontaneously after ten minutes of cardiac massage and artificial respiration, only to die the following night. Convulsions did not occur invariably, however, for three of the dogs died without manifesting them. It is true, that this rapid method of injecting sodium bicarbonate intravenously should never be practiced clinically, but our results serve to emphasize anew the danger that may attend the intravenous injection of an alkali. That convulsions and death may follow this procedure in dogs has already been pointed out by MacCallum, Lintz, Vermilye, Leggett and Boas;[11] and the clinical occurrence of similar manifestations has been described by Blum,[12] Howland and Marriott [13] and Harrop.[14] It would seem natural to assume that the production of an "alkalosis," to use the term of Wilson and his associates,[15] is responsible for the symptoms, but there are certain points which are not in harmony with such an hypothesis. Thus, in our experiments, we found that the acid-base balance of the blood did not serve as a guide to the amount of bicarbonate which would be tolerated. Dog 10 illustrates this, for April 27, with a plasma bicarbonate carbon dioxid of 62 c.c. per 100 c.c. of blood, he suffered no apparent harm from the injection of 5 c.c. per kilogram of a 10 per cent. solution of sodium bicarbonate into the jugular vein; while, on the following day, with a reduction of the plasma bicarbonate carbon dioxid to 52.6 c.c., 4 c.c. per kilogram proved fatal. Likewise, Dog 11 withstood safely an intravenous injection of 5 c.c. per kilogram of a 10 per cent. solution of sodium bicarbonate, the plasma bicarbonate carbon dioxid being 59.4 c.c. per 100 c.c.; but on the following day,

11. MacCallum, Lintz, Vermilye, Leggett and Boas: The Effect of Pyloric Obstruction in Relation to Gastric Tetany, Bull. Johns Hopkins Hosp. **31**:1, 1920.

12. Blum: Les dangers des injections intraveineuses alcalines, Semaine méd. **36**:433, 1911.

13. Howland and Marriottt: Observations upon the Calcium Content of the Blood in Infantile Tetany and upon the Effect of Treatment by Calcium, Quart. J. Med. **2**:289, 1917.

14. Harrop: The Production of Tetany by the Intravenous Infusion of Sodium Bicarbonate, Bull. Johns Hopkins Hosp. **30**:62, 1919.

15. Wilson, Stearns and Janney: The Effect of Acid Administration on Parathyroid Tetany, J. Biol. Chem. **21**:169, 1915.

with a plasma bicarbonate carbon dioxid reduced to 57.4 c.c., a repetition of the injection caused death.

MacCallum and his collaborators observed an increase in the plasma bicarbonate carbon dioxid as high as 119 c.c., without the appearance of convulsions, but the injection was made slowly and they probably used an anesthetic. Collip and Backus [16] also injected large amounts of sodium bicarbonate solution into the veins of dogs without the appearance of convulsions, but the same factors were present here as in the experiments of MacCallum. Blum states that the occurrence of the symptoms may be delayed some hours after the completion of the injection of the alkali, which is hardly in accordance with the view that they are due to a sudden disturbance in the acid-base equilibrium. The suggestion of Blum that the convulsions are the result of a toxic action of the sodium ion seems improbable, because the more readily ionizable sodium chlorid does not produce convulsions when injected in this manner in the form of a 5 per cent. solution, as judged by a single experiment.

To obtain information regarding the third point, namely, that sodium bicarbonate administered in such a way as not to cause the death of the animal does not markedly influence the course of the poisoning, two methods of procedure were adopted; first, the oral method of administering the bicarbonate, and second, the intravenous injection at so slow a rate that a fatal outcome is avoided.

To determine the value of the orally administered alkali, four dogs were given 8 c.c. per kilogram of methyl alcohol after the preliminary injection of 10 mg. morphin sulphate per kilogram. In a very short while, a 2 per cent. solution of sodium bicarbonate was given orally, 50 c.c. per kilogram. Emesis occurred in only one of the dogs, the other three retaining all of the solution thus administered. All four died, as shown in Table 4.

As may be seen from Table 4, treatment with the sodium bicarbonate was instituted promptly and was pursued vigorously. In three cases, all of the bicarbonate administered was retained, emesis not occurring. Unfortunately, however, plasma bicarbonate carbon dioxid determinations were not carried out on these animals, so that it cannot be stated positively that the alkali reserve was kept at a high level, as probable as this is. In order to meet this objection, three dogs were injected with the customary dose of 10 mg. morphin sulphate per kilogram and then given orally 8 c.c. of methyl alcohol per kilogram. These animals were then treated by the slow intravenous injection of 5 per cent. solution of sodium bicarbonate, from twenty to

16. Collip and Backus: The Alkali Reserve of the Blood Plasma, Spinal Fluid and Lymph, Am. J. Physiol. **51**:551, 1920.

ninety minutes being consumed for the injection of the dose of 25 c.c. per kilogram. Vomiting, purging, and mild convulsions occurred, but, on the appearance of such symptoms, the injection was immediately discontinued temporarily, so that death was not caused by the injection in any instance that we could determine. Three of the four animals succumbed, one of these showing a plasma bicarbonate carbon dioxid value of 60.7 c.c. shortly before death. The results are shown in Table 5.

TABLE 4.—RESULTS OF ORAL ADMINISTRATION OF SODIUM BICARBONATE

Number of Experiment	Weight of Dog in Kg.	Dose of Alcohol in C.c. per Kg.	Lapse Before Treatment, Min.	Amount of Sodium Bicarbonate per Gm. in 24 Hours, Gm.	Length of "Survival"
56	12.5	8	88	4.5	24 hours
56-a	8.63	8	75	5.0	24 hours
57	5.68	8	59	5.0	96 hours
58	9.09	8	58	2.5	48 hours

* In every instance, death had occurred some time prior to this; the animals were found dead at the expiration of the time given. It is interesting to note that the animal surviving longest (57) vomited frequently and profusely.

TABLE 5.—RESULTS FROM SLOW INTRAVENOUS INJECTION OF 5 PER CENT. SODIUM BICARBONATE

Number of Experiment	Weight of Dog in Kg.	Dose of Alcohol in C.c. per Kg.	Lapse Before Treatment, Min.	Amount of Sodium Bicarbonate per Gm. in 24 Hours, Gm.	Length of Survival
65	5.7	8	330	1.25	96 hours
67-a	9.8	8	50	1.25	Recovered
68	7.0	8	250	1.25	72 hours

From these experiments that we have carried out on dogs, it is apparent that the resistance of these animals to the poisonous action of methyl alcohol is quite variable, but that the majority will succumb to a subcutaneous or oral dose of 8 c.c. per kilogram. This is in fairly close agreement with the results previous workers have obtained, the "almost always" fatal dose being placed by them a little higher. It must be remembered that there is the possibility of a seasonal variation in the resistance; but this factor is unimportant in the present study, for all of the experiments were carried out at the same season.

While there is a reduction of the reserve alkali of the blood, as determined by the Van Slyke-Cullen method, in most of the animals examined, this is not invariably the case, and the reduction is by no means always commensurate with the severity of the symptoms. A marked reduction may occur in a dog showing only slight evidence of intoxication; while the reverse is occasionally seen, an animal suc-

cumbing to the fatal action of the alcohol and yet preserving a normal alkali reserve.

The rapid method employed by us in administering the bicarbonate is, we grant, entirely unlike the method of administration that would be employed on a human patient; nevertheless, we feel that the disastrous results obtained by it should serve as a warning against the too ready use of intravenous injections of hypertonic solutions of sodium bicarbonate.

Attractive as it is in theory, the results we have obtained by the use of alkaline therapy in the treatment of methyl alcohol poisoning [17] are not encouraging. It is interesting to note that Davis and Whipple [18] were similarly unsuccessful in the employment of sodium carbonate in the treatment of delayed chloroform poisoning.

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17. Gettler and St. George: Wood Alcohol Poisoning, J. A. M. A. **70**: 145 (Jan. 19) 1918.

18. Davis and Whipple: The Influence of Drugs and Chemical Agents on the Liver Necrosis of Chloroform Anesthesia, Arch. Int. Med. **23**:636 (June) 1919.

THE CONSTANCY OF THE VOLUME OF THE BLOOD PLASMA *

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INTRODUCTION

Until about the middle of the nineteenth century no observations as to the total blood mass in the human body were presented by either clinicians or physiologists. In 1854, Welcker [1] attempted to determine the quantity of blood in the bodies of two criminals by means of a washing out method, and he established as normal the figure of $\frac{1}{13}$ of the body weight, which has remained the standard commonly adopted up to the present time. Even today, after a considerable series of investigations of this problem by various workers, figures given for the total blood volume in man are approximate and not absolute. The results usually quoted vary from $\frac{1}{10}$ to $\frac{1}{21}$ of the body weight. This uncertainty regarding the actual amount of circulating blood is largely due to technical difficulties. Clinical methods for determining the blood volume now available, however, yield results consistent enough to furnish a figure approximating the true volume and to afford data from which relative changes in the blood mass may be determined.

It is the purpose of this paper to show that the plasma volume in man, in contradistinction to the total blood volume, tends to be a physiologic constant, except under certain stated conditions. The evidence consists of data obtained by blood volume determinations in five normal and twenty-five abnormal individuals. With reference to changes in the blood, the latter cases include examples of extreme variations in total blood volume, corpuscle content, and so forth.

METHOD

The total mass of circulating blood may be determined by a number of indirect methods. For recent reviews of these, reference may be made to the papers of Keith, Rowntree and Geraghty [2] and Salvesen.[3]

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* From the Medical Clinic of the Massachusetts General Hospital. This is Study 6 of a series of studies of the physiology and pathology of the blood from the Harvard Medical School and allied hospitals.

1. Welcker, H.: Prager Vrtljschr. **4**:145, 1854.
2. Kieth, N. M.; Rowntree, L. G., and Geraghty, J. T.: Arch. Int. Med. **16**:547 (Nov.) 1915.
3. Salvesen, H.: J. Biol. Chem. **40**:109, 1919.

The vital red method was used for the present study. In principle it consists in the colorimetric determination of the dilution in the plasma of a known amount of a dye, vital red, which has been injected intravenously and allowed to circulate for a period of four minutes, when the sample of blood required for the determination is withdrawn. Having obtained the plasma volume in this manner, the total volume may be calculated from the proportion of corpuscles to plasma as shown by the hematocrit.

Remarkably constant results have been obtained with this method in man by Keith, Rowntree and Geraghty, the total blood mass measuring $\frac{1}{11.4}$ of the body weight in a series of eighteen normal men.[2] The same method as modified and used in dogs by Dawson, Evans and Whipple,[4] and the acacia method of Meek and Gasser,[5] show close agreement with each other, and the values reported by these observers for normal dogs per kilogram of body weight approximate those found in man.

Total blood volume determinations have also been made in a variety of conditions with the carbon monoxid method, a method which in the hands of Haldane and Smith[6] gave values ranging from $\frac{1}{30}$ to $\frac{1}{16}$ of the body weight in fourteen cases examined. The value $\frac{1}{30}$ was obtained in a patient of an extremely obese type. Later, Haldane and Douglas[7] made repeated observations with the carbon monoxid method on each other and found a mean value for the total blood volume from which variations did not exceed 8 per cent., in excess or deficiency, except in one instance for each subject. Salvesen[8] obtained an average value for normal men of $\frac{1}{16.8}$ of the body weight, and Plesch[8] found $\frac{1}{18}$ as an average value in four cases with the same method. In anemic conditions Lorrain Smith[9] found values in chlorosis of $\frac{1}{9.2}$ of the body weight and $\frac{1}{8.9}$ for pernicious anemia; volumes which represent enormous increases over the values obtained for normals by the carbon monoxid method. Finally, Douglas[10] secured constant results in rabbits which agreed closely with the Welcker method, approximating $\frac{1}{21}$ of the body weight in male animals.

The difference in results between the vital red and carbon monoxid methods is not easily explained, but an important consideration concerning it will be found at the end of this paper. The variability in

4. Dawson, A. B.; Evans, H. M., and Whipple, G. H.: Am. J. Physiol. **51**:232, 1920.
5. Meek, W. J., and Gasser, H. S.: Am. J. Physiol. **47**:302, 1918.
6. Haldane, J. S., and Smith, J. L.: J. Physiol. **25**:331, 1900.
7. Douglas, C. G.; Haldane, J. S.; Henderson, Y., and Schneider, E. C.: Phil. Tr. Roy. Soc., London, Series B, **203**:195.
8. Plesch, J.: Ztschr. f. Exper. Path. u. Therap. **6**:380, 1909.
9. Smith, J. L.: Proc. Physiol. Soc., Dec. 9, 1899, p. 6.
10. Douglas, C. G.: J. Physiol. **33**:493, 1906.

results with the carbon monoxid method may be more apparent than real, as Boycott [11] suggests, but it seems probable that the values generally accepted for the blood volume in anemia, based on Smith's figures, are too great as may be seen by results in similar cases quoted here.

There remains to be mentioned the conception of Dreyer and Ray [12] that the volume of the blood in mammals is directly proportional to the surface area of the body. They believe that the practice of expressing blood volume as a per cent. of body weight is erroneous and misleading, and that it should be expressed in the formula $B.V. = \frac{B.W.^{0}}{K}$ in which K is a constant which must be worked out for each species. The formula has recently been extended to application in man and used by Bazett [13] in determining the amount of blood lost by operative procedures. As adopted for man the formula is $B.V. = \frac{B.W.^{.72}}{0.67}$. This formula yields a blood volume in man equivalent to approximately $\frac{1}{9.3}$ of the body weight, a higher figure than has been obtained by any of the other methods.

RESULTS IN NORMAL INDIVIDUALS

It is unfortunate that more figures concerning the blood plasma volume in normal men are not available. At present, in addition to the data presented here, the figures of Keith, Rowntree and Geraghty [2] alone may be referred to.

In Table 1 are presented the data of the five normal individuals in this series.[14] The total volume is $\frac{1}{12.2}$, or 8.7 per cent. of the body weight, as compared with 8.8 per cent. as found in the series of Keith, Rowntree and Geraghty. The average plasma volume expressed as a fraction of the body weight is $\frac{1}{19.6}$, or 5.1 per cent., which agrees closely with the figure of $\frac{1}{19.4}$ in the above series. Data of this type as well as that obtained in animals by the vital red method [4] reveal only slight variations in the plasma volume in normal individuals per kilogram of body weight. An investigation by Bogert, Underhill and Mendel [15] concerning the regulation of the blood volume after injections of saline solutions leads to the same conclusion.

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11. Boycott, A. E.: J. Path. & Bacteriol. **16**:485, 1911.
12. Dreyer, G., and Ray, W.: Phil. Tr. Roy. Soc., London **201**:159, 1910.
13. Bazett, M. C.: Medical Research Committee. Wound Shock and Hemorrhage, Report 5, 1919.
14. It must be emphasized again that the figures presented in the tables in this paper are not put forward as absolute values. Their value lies rather in the consistency of results obtained with the vital red method, and they offer a working basis for problems concerned with blood volume. The vital red method and modifications of it are the only methods available by which the plasma volume is directly estimated.
15. Bogert, L. J.; Underhill, F. P., and Mendel, L. B.: Am. J. Physiol. **41**:189, 1916.

RESULTS IN POLYCYTHEMIA

In three cases of polycythemia vera, as shown in Table 2, the average total volume is 13.2 per cent., or $\frac{1}{7.3}$ of the body weight, the increase above the normal figure (approximately $\frac{1}{12}$) being entirely due to the great increase in the total number of corpuscles which average 2.5 times the number found in normal men. The plasma fraction of the body weight varied from $\frac{1}{16.2}$ to $\frac{1}{21.2}$, the average being $\frac{1}{19.3}$. Thus, while the plasma volume in polycythemia is the same as in normal individuals, the total blood per kilogram, in the cases studied, averages 47 c.c. more than in the normal. The relatively high plasma volume in Case 8 is difficult to explain. This patient had had a long course of treatment with radium and the roentgen ray.

RESULTS IN PERNICIOUS ANEMIA

The seven cases of pernicious anemia have an average plasma volume of 4.9 per cent., or $\frac{1}{20.5}$ of the body weight, and a total volume of 5.7 per cent., or $\frac{1}{17.3}$ of the body weight (Table 3). The first four cases, with hemoglobin values ranging from 43 to 59, per cent., have plasma volumes averaging 5.4 per cent., or $\frac{1}{18.5}$ of the body weight. Cases 13 and 14 have an average plasma volume of 4 per cent., or $\frac{1}{25}$ of the body weight. It will be observed that in each of these cases the hemoglobin is below 30 per cent., which may account for the low plasma volumes. The condition seems to parallel that found after severe hemorrhage.[16] The last case, with a relatively high hemoglobin and high count of red corpuscles, has a plasma volume of 5.1 per cent., or $\frac{1}{19.4}$ of the body weight. It is apparent, therefore, that but little variation occurs in the plasma volume in primary anemia. The reduction in the total volume of blood in cases with hemoglobin above 30 per cent. is due entirely to the low content of corpuscles. The average volume of corpuscles is $\frac{1}{5}$ of that found for normals and $\frac{1}{13}$ of the number in polycythemia. A total mass of 270 c.c. of corpuscles, as in Case 8, contrasts greatly with the usual quantity of about 2,000 c.c. found in the normal.

RESULTS IN MISCELLANEOUS CASES

The group of miscellaneous cases includes one case (Case 22) of cardiac failure of the congestion type, with anasarca, and two cases (Cases 16 and 17) of chronic nephritis with extensive edema. The average results presented in Table 4 show, so far as the plasma is concerned, a remarkably small deviation from the normal. The average plasma value is 4.9 per cent., or $\frac{1}{20.3}$ of the body weight.

16. Robertson, O. H., and Bock, A. V.: J. Exper. M. **29**:139, 1919.

TABLE 1.—Data for Five Normal Individuals *

Case No.	Sex*	Weight in Kilos	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Cent. of Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total Blood per Cent. of Body Weight	Total O_2 Capacity in C.c.	Per Cent. Hb. Calculated from O_2 Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Trillions
1	♂	68	57	91	3,628	1/17.3	5.7	2,130	5,758	1/10.9	9.1	1,372	128	4.8	27.6
2	♂	82	46	76	3,731	1/21.9	4.5	2,487	6,218	1/13.1	7.6	1,442	122	4.8	30.0
3	♀	55	54	83	2,990	1/18.4	5.4	1,610	4,600	1/11.9	8.3	901	108	4.0	18.4
4	♂	67	50	82	3,343	1/20	5.0	2,137	5,480	1/12.2	8.2	1,205	119	5.2	28.6
5	♂	69	49	77	3,380	1/20	5.0	1,901	5,281	1/13	7.7	.....	...	5.0	26.4
Average		67	51	81	3,414	1/19.6	5.1	2,053	5,467	1/12.2	8.2	.....	119	4.8	26.2

* In this and the following tables, ♂ indicates male and ♀ female.

TABLE 2.—Data for Three Cases of Polycythemia

Case No.	Sex	Weight in Kilos	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Cent. of Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total Blood per Cent. of Body Weight	Total O_2 Capacity in C.c.	Per Cent. Hb. Calculated from O_2 Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Trillions
6	♂	60.5	47	122	2,820	1/21.4	4.7	5,725	8,545	1/7	14.3	2,851	180	8.8	75.1
7	♂	54	47	134	2,570	1/21	4.8	4,772	7,342	1/7.3	13.7	2,934	198	10.3	75.6
8	♀	49	61	128	3,013	1/16.2	6.1	3,264	6,277	1/7.8	12.8	1,299	112	8.3	51.9
Average		54.5	51.6	128	2,824	1/19.3	5.1	4,587	7,388	1/7.3	13.7	2,364	163	9.1	67.6

TABLE 3.—Data for Seven Cases of Pernicious Anemia

Case No.	Sex	Weight in Kilos	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Cent. of Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total Blood per Cent. of Body Weight	Total O_2 Capacity in C.c.	Per Cent. Hb. Calculated from O_2 Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Trillions
9	♀	43.5	59	70	2,597	1/17.2	5.9	468	3,055	1/14.2	7.0	284	50	1.7	5.1
10	♀	43	54	64	2,329	1/18.3	5.4	411	2,740	1/15.7	6.3	300	59	1.8	4.9
11	♀	45	48	54	2,189	1/20.5	4.9	270	2,459	1/18.2	5.4	197	43	1.2	3.0
12	♂	50	54	61	2,729	1/18.3	5.4	337	3,066	1/16.3	6.1	266	40	1.3	4.0
13	♀	55	38	44	2,136	1/25.7	3.8	264	2,400	1/23	4.3	125	28	1.1	2.7
14	♂	71	41	44	2,933	1/24.2	4.1	221	3,154	1/22.5	4.4	139	24	0.67	2.1
15	♂	59	51.5	72.5	3,040	1/19.4	5.1	1,241	4,281	1/13.7	7.3	583	73	3.2	13.9
Average		52.3	49.3	58.5	2,555	1/20.4	4.9	459	3,022	1/17.3	5.7	270	47	1.6	5.1

Consideration of the fact that the method used in determining the plasma volume and the complex nature of the problem itself leads to the conclusion that the results in these cases are quite identical with those found in the normal. It is to be noted again that the smaller total volume of 7.1 per cent., or $\frac{1}{14}$ of the body weight, is due to the diminished volume of corpuscles associated with the anemia present in some of the cases.

RESULTS IN DIABETES MELLITUS

Eight cases of diabetes mellitus afford an interesting study which will be made the subject of a later report. For the purpose of this paper it is important, only, to point to the average results as shown in Table 5. The average plasma value per kilo is 48 c.c., 4.8 per cent., or $\frac{1}{20.8}$ of the body weight. The variations of plasma volume in individual cases are greater than were found in other conditions, but the general average for the plasma volume in diabetes is close to the normal. Notwithstanding this fact, the problem of the plasma volume in diabetes, particularly during the stage of severe acidosis, remains to be worked out.

THE EFFECT OF EDEMA ON THE PLASMA VOLUME

It is the prevailing view in the literature that rapid alterations in body weight due to the water content of the body are associated with changes in the blood volume. With sudden increase in weight of the body the blood is said to become hydremic and with sudden losses it becomes more concentrated.[17] For example, Krehl [18] states that there is no reason why the blood should not become edematous as well as other tissues. He believes that a real hydremic plethora accompanies cardiac and renal diseases, and thinks there is no reason a priori why an increase in the total quantity of blood should not take place. Von Noorden,[19] on the other hand, after reviewing similar considerations, concludes that one cannot be certain of such a plethora because of the little certain knowledge of the watery content of the blood.

While it is possible that hydremia or hydremic plethora, as it is usually called, may be present in some conditions, it certainly is not found in the usual course of events, and its occurrence must be regarded as infrequent except possibly as a terminal affair. In Table 6 is presented evidence in three cases of edema to show that the relation of the blood plasma to the body weight remains undisturbed in such conditions. In Case 16, a chronic glomerulonephritis in a girl,

17. Barker, L. F.: Monographic Medicine **1**:561, 1916.
18. Krehl, L.: Clinical Pathology, Ed. 2, 1907, p. 172.
19. Von Noorden, C.: Metabolism and Practical Medicine **2**: 1907.

TABLE 4.—Data for Seven Miscellaneous Cases

Case No.	Sex	Diagnosis	Weight in Kilos	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Cent. of Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total Blood per Cent. of Body Weight	Total O_2 Capacity in C.c.	Per Cent. Hb. Calculated from O_2 Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Trillions
16	♀	Chronic nephritis	54.5	40	47	2,200	1/24.7	4.0	387	2,587	1/21	4.7	217	45	2.0	5.7
17	♀	Chronic nephritis	40	57	76	2,291	1/17	6.0	764	3,055	1/33	7.7	360	63	3.3	10.0
18	♂	Chronic nephritis	65	47	67.5	3,117	1/20.8	4.8	1,273	4,390	1/14.8	6.7	758	98	4.7	20.5
19	♂	Myasthenia gravis	63	46.6	78	2,933	1/21.5	4.6	2,038	4,971	1/12.7	7.8	1,144	123	5.3	26.6
20	♀	Secondary anemia	60.5	56	74	3,400	1/17.8	5.6	1,073	4,473	1/13.5	7.4	476	57	4.4	19.6
21	♀	Secondary anemia	53.5	53.4	72	2,800	1/18.7	5.3	953	3,813	1/14	7.1	368	52	4.0	15.5
22	♂	Cardiac failure	72.2	46	81	3,333	1/21.6	4.6	2,514	5,847	1/12.3	8.2	1,231	114	5.0	29.2
Average.....			58.4	49.4	70.7	2,876	1/20.3	4.9	1,183	4,162	1/14	7.1	670	79	3.9	18.3

TABLE 5.—Data for Eight Cases of Diabetes

Case No.	Weight in Kilos	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c	Total Plasma Fraction of Body Weight	Total Plasma per Cent. of Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total Blood per Cent. of Body Weight	Total O_2 Capacity in C.c.	Per Cent. Hb. Calculated from O_2 Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Trillions	Per Cent. Plasma Sugar
23	41.5	57	91	2,366	1/17.5	5.7	1,419	3,784	1/11.2	8.9	770	110	4.6	18.4	0.22
24	54.5	40	62	2,200	1/24.7	4.0	1,163	3,363	1/16.2	6.1	723	116	4.6	15.7	0.38
25	62	40	61	2,841	1/26.6	3.7	1,278	3,759	1/16.5	6.0	969	139	3.7	13.9	0.24
26	35.5	62	82.5	2,200	1/16	6.2	733	2,933	1/12.1	8.2	475	87	3.3	9.7	0.39
27	47	53	85	2,500	1/18.8	5.3	1,530	4,030	1/11.6	8.7	790	110	4.1	16.6	0.19
28	50	42.5	66.5	2,136	1/23.4	4.2	1,201	3,337	1/14.9	6.7	800	139	6.0	20.0	0.26
29	70	42.7	66.7	2,988	1/23.4	4.2	1,700	4,688	1/14.9	6.7	1,000	126	5.12	24.0	0.26
30	43	56.8	90	2,444	1/17.6	5.6	1,435	3,879	1/11.9	8.3	....	...	4.5	17.6	0.22
Average	50.4	48	75.5	2,414	1/20.8	4.8	1,308	.....	1/13.5	7.3	812	118	4.6	17.0	

aged 16, after a loss of 13.5 kg. in weight and disappearance of all visible edema, the plasma volume per kilogram of body weight remained unchanged. No attempt is made to explain the relatively low plasma volume in this patient, who also suffered from a severe anemia. In Case 28, diabetes mellitus in a boy, aged 17, after the addition of 4 kg. in weight while on a forced fluid and increased salt intake, there was essentially no alteration in the plasma volume per kilogram of weight. In Case 22, a man, aged 75, with cardiac failure of the congestion type, and with anasarca at the time of the first observation, the figures show an apparent change in plasma volume, which, however, is only 8 per cent. and is within the margin of error. Keith, Rowntree and Geraghty [2] found similar results in a case of nephritis with edema.

Boycott [20] found that the edema which may be brought about by the administration of water to animals with uranium nephritis involved the blood as well as the rest of the tissues. The blood dilution, determined by changes in hemoglobin, in such animals was associated with fluid in the pleural and peritoneal cavities and with edema of the loose connective tissue in general. The effect on the blood volume of intravenous injection of dextrose and of sodium chlorid was found to be more prolonged in nephritic than in normal rabbits.[21] It is possible that in man the edema associated with acute nephritis might be reflected for a time in dilution of the blood plasma, but in subacute and chronic conditions the body adjustments seem to compensate for the disturbance in fluid balance, and the blood does not share in the general edema of the tissues.

A recent theory by McLean [22] concerning the mechanism of edema is worthy of note in the present discussion. The usual idea of edema is that the excess fluid represents an accumulation of fluid in the body, a process static in nature. McLean points out that the condition cannot be static in nature but that there must be a constant interchange of fluid and dissolved substances in edema as well as under normal conditions between the blood, tissue fluids, and contents of lymph channels in order to maintain cellular life. The condition must be regarded as an equilibrium, as Meltzer has also suggested. As the plasma volume determinations in cases of edema presented above have indicated, there is no shift of increased fluid into the blood in edema, but the balance between plasma and tissue fluids is maintained through such an interchange of fluid and dissolved substances as to maintain the fluid phase of the blood at about its normal level.

A summary of the above data is presented in Table 7.

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20. Boycott, A. E.: J. Path. & Bacteriol. **18**:11, 1913.
21. Boycott, A. E., and Douglas, C. G.: J. Path. & Bacteriol. **19**:221, 1914.
22. McLean, F. C.: Personal communication.

TABLE 6.—Data Showing Influence of Edema on Blood Plasma

Case No.	Sex	Date	Diagnosis	Weight in Kilos	Edema	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Cent. of Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total Blood per Cent. of Body Weight	Total O_2 Capacity in C.c.	Per Cent. Hb. Calculated from O_2 Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Trillions
16	♀	Jan. 9	Chronic nephritis	54.5	+++	40	47	2,200	1/24.7	4.0	387	2,587	1/21	4.7	217	45.2	2.0	5.7
16	♀	Jan. 24	Chronic nephritis	46	++	41	50	1,900	1/24.2	4.1	417	2,317	1/19.8	5.0	202	60.6	2.5	5.9
16	♀	Feb. 3	Chronic nephritis	41	0	41	48	1,690	1/24.2	4.1	275	1,965	1/20.8	4.8	223	61.5	2.4	4.7
28	♂	Jan. 23	Diabetes	50	0	42.5	66.5	2,136	1/23.4	4.2	1,201	3,337	1/15	6.6	861	139.0	6.0	20.0
28	♂	Jan. 27	Diabetes	54	±	44	66.5	2,376	1/22.7	4.4	1,221	3,592	1/15	6.6	736	111.0	5.0	17.8
22	♂	Apr. 16	Cardiac failure	72.2	+++	46	81	3,333	1/21.6	4.6	2,514	5,847	1/12.3	8.1	1,231	114.0	5.0	29.2
22	♂	Apr. 20	Cardiac failure	61.3	±	51.6	91	3,170	1/19.3	5.1	2,112	5,582	1/10.9	9.1	1,271	112.7	5.0	27.9

TABLE 7.—Average Results

No. of Cases	Diagnosis	Weight in Kilos	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Cent. of Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total Blood per Cent. of Body Weight	Total O_2 Capacity in C.c.	Per Cent. Hb. Calculated from O_2 Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Trillions
5	Normal	67	51	81	3,414	1/19.6	5.1	2,053	5,467	1/12.2	8.2	1,230	119	4.8	26.2
3	Polycythemia	54.5	51.6	128	2,824	1/19.3	5.1	4,587	7,388	1/ 7.3	13.7	2,364	163	9.1	67.6
7	Pernicious anemia	52.3	49.3	58.5	2,555	1/20.4	4.9	459	3,022	1/17.3	5.7	270	47	1.6	5.1
7	Miscellaneous	58.4	49.4	70.7	2,876	1/20.3	4.9	1,183	4,162	1/14	7.1	670	79	3.9	18.3
8	Diabetes	50.4	48	75.5	2,414	1/20.8	4.8	1,308	3,721	1/13.5	7.3	812	118	4.6	17.0

THE EFFECT OF HEMORRHAGE ON THE PLASMA VOLUME

Acute hemorrhage results in an immediate mechanical reduction of the total blood volume. If the hemorrhage is not too great, and if a reserve supply of tissue fluids is available, a flow of fluids from the tissue spaces into the circulation occurs during the process of hemorrhage so that the blood plasma may be diluted to its normal level as rapidly as possible. In a case of controlled hemorrhage four conditions may prevent a return of the plasma volume to normal: (1) lack of adequate fluid reserve in the tissues, as was found frequently

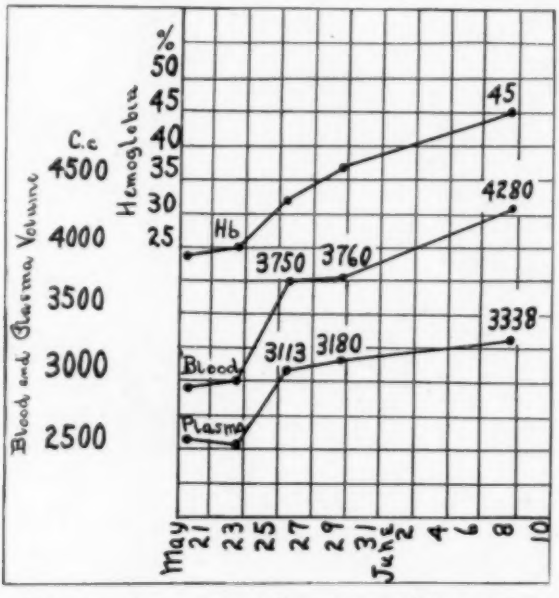

Fig. 1.—This chart is constructed from data published by Robertson and Bock, their Case 4, to show the rapid recovery of the plasma volume to normal after hemorrhage, and the gradual restoration of the total blood volume.

in soldiers wounded in action; (2) lack of adequate fluid intake by the alimentary tract; (3) a state of shock which in some degree always accompanies moderate and severe hemorrhage and in which the regulation of fluid balance between the blood and tissue fluids is disturbed; (4) a reduction in total hemoglobin below 25 per cent., as was shown by Robertson and Bock.[16] In the last condition, as long as the hemoglobin remains at or below 25 per cent., the plasma volume will remain below normal and no known measures can change this condition except the addition of more hemoglobin. If none of the four conditions above

named are present, the plasma tends to assume normal proportions in a comparatively short time and will then remain at the level normal for the given individual. The total blood volume, however, will remain below normal until the processes of blood regeneration have restored the normal quantity of corpuscles. Figure 1, constructed from Case 4, of Robertson and Bock, illustrates this mechanism of recovery in a case of severe hemorrhage. With a hemoglobin value of 24 per cent., the plasma remained at 2,600 c.c. Accompanying a rise in hemoglobin to 33 per cent. the plasma increased to 3,113 c.c. Two days later the hemoglobin was 38 per cent. and the plasma 3,180 c.c. Nine days later, when the hemoglobin had reached 45 per cent., the

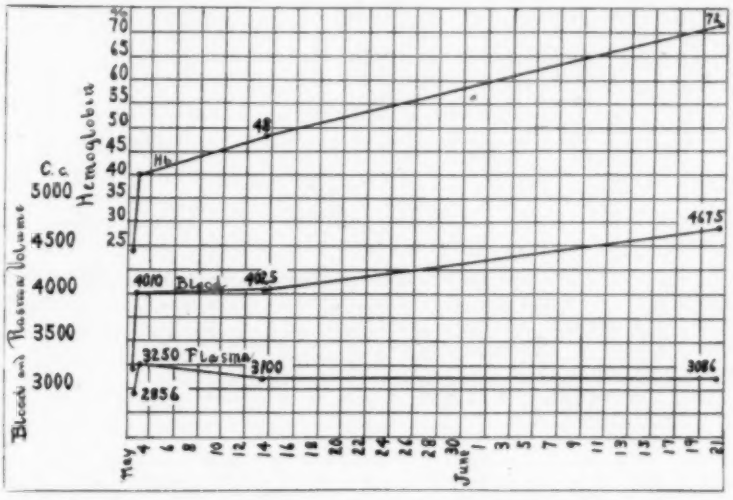

Fig. 2.—Also from Robertson and Bock, their Case 5, showing the constant level of the plasma volume as the total volume increases by the addition of red corpuscles.

plasma was 3,338 c.c. and the total volume had increased 1,300 c.c. since the original observation. Figure 2, Case 5, also from the same authors, shows a reduced plasma of 2,856 c.c. as a result of a hemorrhage which was brought up to normal by transfusion. Subsequent determinations show approximately no change in the figures. The total volume increased 650 c.c.

Figure 3 is the record of a case showing reaction following hemorrhage from a gastric ulcer. The first observation was made approximately twelve hours from the time hemorrhage apparently stopped. The plasma curve as represented shows the plasma reduction at once after hemorrhage, and after dilution to the usual level for this patient.

No further change in plasma volume occurred although the total blood volume steadily increased by reason of the addition of new red corpuscles.

Figure 4 represents the findings in another case of gastric ulcer, the observations beginning three days after hemorrhage had ceased and at a time when the plasma had already reached a normal level by dilution. The patient was transfused because of the low hemoglobin figure of 32 per cent. The plasma volume prior to transfusion was 2,685 c.c., and subsequent determinations showed very little change from this figure.

As a result of experimental hemorrhage in animals, it has frequently been reported that overdilution of the blood occurs by absorp-

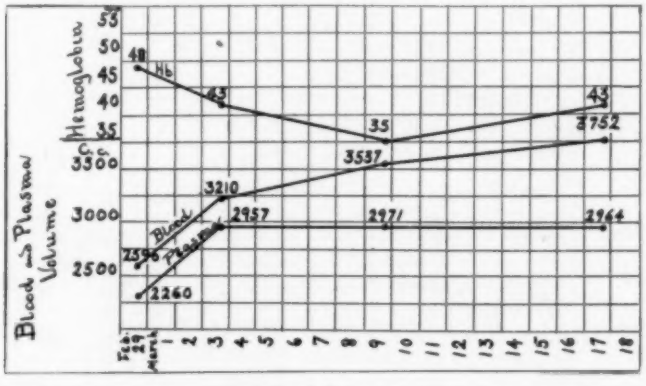

Fig. 3.—Showing the reaction of the blood following hemorrhage from a gastric ulcer, observations beginning twelve hours after the hemorrhage stopped. The plasma volume after dilution to normal, remains constant. Incidentally, this case illustrates a falling color index often seen in blood regeneration after hemorrhage.

tion of fluid from the tissues with the result that the total volume immediately subsequent to the absorption period is greater than before the hemorrhage occurred. For a discussion of this question reference may be made to the work of Boycott and Douglas.[23] Observation of the reaction from hemorrhage in man has failed to show that overdilution takes place and it may be said that this condition does not occur under the conditions which usually obtain. It should be understood that the blood volume determinations referred to in the work of Boycott and Douglas are "relative blood volumes" in the sense

23. Boycott, A. E., and Douglas, C. G.: J. Path. & Bacteriol. **13**:256, 1908.

that they are calculated from changes in the hemoglobin. Actual blood volume determinations made under the same experimental conditions employed by these authors would be interesting.

CHANGES IN THE PLASMA VOLUME IN CERTAIN CLINICAL CONDITIONS

While increase or reduction in the plasma volume does not occur in disease to any great degree, certain conditions are associated with concentration or loss of blood which remain to be mentioned, since they constitute exceptions to the general rule. The exceptions are

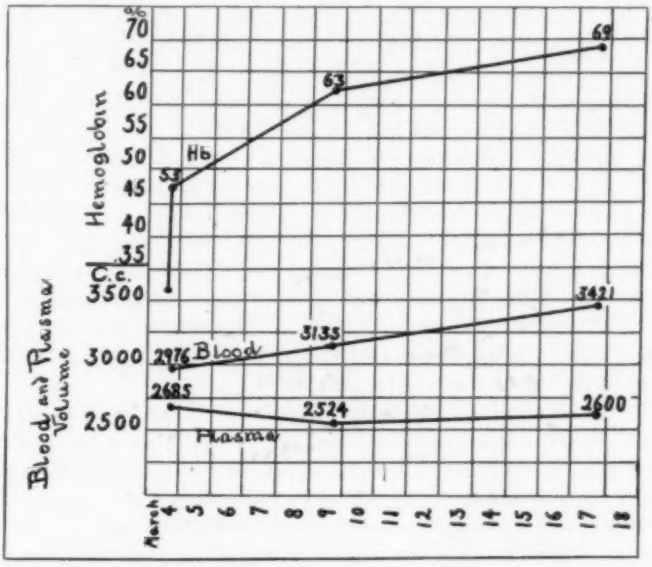

Fig. 4.—Observations begun three days after hemorrhage from gastric ulcer. Initial dilution of plasma to normal had already occurred. The effect of transfusion in this case on the plasma volume is negative, whereas the hemoglobin increased from 32 to 53 per cent.

concerned with conditions in which there is great fluid loss either directly from the circulation or through a more gradual loss of the body reserve fluid. Aside from acute hemorrhage and shock already mentioned, such conditions as acute edema of the lungs, excessive sweating, and diarrhea of severe type as seen in infants and in Asiatic cholera are outstanding examples. Cunningham [24] observed a patient having edema of the lungs, in whom the oxygen capacity of

24. Cunningham, T. D.: Personal communication.

the blood at the height of the attack was 25 volumes per cent. as compared to the man's normal oxygen capacity of 19 volumes per cent. Such a change in the oxygen capacity per unit volume of blood, occurring in a short time, suggests extensive contraction of the plasma volume. This finding is in agreement with experimental work on the effects of poison gas in rabbits by Haldane, Meakins and Priestley.[25] They found, at necropsy, extensive edema of the lungs which was believed to be associated with a corresponding depletion of the blood plasma.

Many observers have reported changes in the peripheral blood indicating concentration as a result of great sweating incident to work and exercise. No blood volume determinations are reported in such conditions except by Schneider and Havens.[26] These workers found the usual changes in the peripheral blood, notable increase in the percentage of hemoglobin, red corpuscle count and rise in specific gravity, which have been observed by others repeatedly. They also found, however, that abdominal massage for a brief period increased the number of red blood cells in the peripheral blood in about the same proportions as occurred after vigorous exercise. The logical deduction that they make is that a reserve store of corpuscles is present in the splanchnic area during comparative inaction which is called into the circulation by exercise. They found no alteration in the blood volume by the carbon monoxid method. Some doubt may, therefore, be entertained concerning fluctuations of the plasma volume under conditions of work and exercise.

The dehydration of the body fluids as a result of diarrhea and cholera is well known to clinicians. Marriott[27] has recently called attention to a condition in infants in which he described changes in the blood which simulate those found in hemorrhage and shock. The thickness of the blood in cholera requires little comment. In this condition dehydration of the tissues proceeds to an extreme state in an effort to meet the requirements of the blood plasma but concentration of the blood inevitably occurs.

The effect of altitude on the total blood volume has also been studied in both man and animals. The results in man indicate that the final alterations consist in a variable increase of red corpuscles and a slight increase in the total blood volume. Douglas, Haldane, Henderson and Schneider[7] report an additional increase in the blood volume after descent from Pike's Peak, and offer as an explanation

25. Haldane, J. S.; Meakins, J. C., and Priestley, J. G.: Personal communication from J. C. Meakins.

26. Schneider, E. C., and Havens, L. C.: Am. J. Physiol. **36**:239, 1915.

27. Marriott, W. McK.: Paper read before Am. Soc. for Clin. Investigation. 1919.

a probable dilution of the blood plasma in order to decrease the viscosity of blood in which polycythemia had occurred as a result of residence at the summit of Pike's Peak. Such an interpretation does not coincide with present findings in cases of polycythemia vera in which the problem of viscosity is not adjusted by an increase in the plasma volume. Whatever the mechanism of adjustment may be, it is certain that such changes in volume are temporary in persons who have resumed residence at the usual altitudes.

In the present discussion may be included a condition of another type, namely obesity, in which there is known to be a reduction in the total blood volume. Haldane and Smith [6] report one case of extreme obesity having a volume of 1/30 of the body weight. Keith, Rowntree and Geraghty [2] present six cases having an average plasma volume of 37.1 c.c. per kilogram, or 3.8 per cent. of the body weight. There is no evidence that fluctuations in the plasma volume occur in this condition.

DISCUSSION

In relation to the present series of cases, certain additional results in the work of Keith, Rowntree and Geraghty [2] should be mentioned. They found an increased blood volume in the latter months of pregnancy in twelve cases. The average blood volume was 9.56 per cent. and the average plasma volume 5.7 per cent. After labor the blood volume was 9 per cent. and the plasma volume 4.9 per cent. of the body weight. Such results are in accord with volume findings in pregnancy in animals, but the increase found in women cannot be considered very great and Williams [28] has attached very little significance to it.

With respect to anemia, in ten cases they found three with abnormally high plasma volumes and in six the plasma values were considered slightly higher than normal. The average in eight cases was 56 c.c. per kilogram of body weight. Of three cases of pernicious anemia, two were found to have normal plasma values, 54 c.c. and 53 c.c. per kilogram, while the third had 72 c.c. It is difficult to harmonize the finding of such a high plasma volume in anemia. At variance also with the results obtained in anemia in the present series is the work of Lorrain Smith,[9] who found that in chlorosis and in pernicious anemia the blood volume is greatly increased. For a patient with chlorosis weighing 44.5 kg. the volume found was 6,181 c.c., or 139 c.c. per kilogram of body weight. In a case of pernicious anemia the total volume found was 6,500 c.c., or 112 c.c. per kilogram.

28. Williams, J. W.: Contributions to Medical and Biological Research. Dedicated to Sir William Osler. **2**:1238, 1919.

In each instance the volume is comparable only to that found in polycythemia. In the case of chlorosis the total oxygen capacity was 418 c.c., which is not unlike that of Case 20 of the present series, a patient having secondary anemia of chlorotic type, whose oxygen capacity was 476 c.c. and whose total volume was 4,473 c.c., or 74 c.c. per kilogram. Likewise the case of pernicious anemia reported by Smith, with a total oxygen capacity of 195 c.c., may be compared to Case 12 of the present series, in which the total oxygen capacity was 266.4 c.c. and the total volume was 3,066 c.c., or 61 c.c. per kilogram. The results of the present investigation indicate that the blood volume is diminished in anemia in direct proportion to the decrease in corpuscles.

Of the other conditions reported by Keith, Rowntree and Geraghty, plasma values on the lower limit of normal were found as an average result in thirteen cases of chronic nephritis and hypertension, the average plasma volume being 42.8 c.c. per kilogram. In scattered cases of diabetes emaciation, myocardial insufficiency, aneurysm of the arch, chronic bronchitis, neurasthenia, and so forth, the plasma values were within the normal range.

It is important to remember that in conditions of chronic anemia, for example, no device exists for increasing the fluid volume of the blood beyond the level already attained by the patient, providing a normal tissue fluid reserve is present. Every such patient who has even a moderate fluid intake daily will have an optimum total blood plasma. Lindeman [29] supposed that by forcing food and fluids in cases of pernicious anemia the blood volume was thereby increased. He wrote that a patient with a large blood volume will bear a greater degree of anemia without experiencing palpitation of the heart or roaring in the ears. When the blood volume is small he thought that a less degree of anemia would produce a greater degree of exhaustion. These assumptions have not been confirmed. When symptoms are present in such cases the need is for more hemoglobin, which is the only factor that will bring relief.

Finally, a suggestion may be made concerning the relative values of blood volume methods. There is a belief that dilution of the blood as shown by changes in the hemoglobin percentage is a reliable method of studying blood volume changes. Bogert, Underhill and Mendel [15] recently emphasized the constancy of the hemoglobin per unit of circulating blood, and Scott [30] concluded that large masses of corpuscles are not held in the capillaries of any organ. The work of

29. Lindeman, E.: J. A. M. A. **70**:1292 (May 4) 1918.
30. Scott, F. H.: J. Physiol. **50**:157, 1916.

Schneider and Havens [26] and of Lamson,[31] however, indicates that such a storage of large numbers of red cells does occur in the body and that they may readily be shifted into the peripheral circulation as, for example, by exercise or by administration of epinephrin. Clinical observation has shown that great shifts may occur in the red corpuscle count in diabetics in short periods of time. It seems, therefore, in view of the present uncertain status of our knowledge with respect to the existence of red corpuscle reservoirs, that methods for the determination of blood volume which depend on dilution of whole blood, as well as any other methods employing the red corpuscles primarily, are not theoretically sound. And when one reviews the possible variations in the total corpuscle content of the body, which in this series ranged from two trillions to seventy-five trillions, the possibility for error in such methods is obvious. On the other hand, the plasma volume is relatively a fixed constant, its fluctuations must be limited to a very narrow range and, therefore, methods by which the plasma volume can be directly determined seem to be subject to the smallest number of discrepancies and afford the most accurate results.

Theoretically, there is a mass of data, chiefly physicochemical in nature, that suggests the necessity for a stable plasma volume. The physicochemical relations existing between the blood and tissues of the body form a series of complex phenomena that is disturbed only with difficulty; the effort of the organism, as a whole, is to seek an equilibrium between plasma and cells, although, as Henderson [32] pointed out, equilibrium is never actually attained within the organism. It seems reasonable to suggest that the plasma volume must be free from great alterations from the normal, in quantity, if cellular activity is to proceed at an optimum rate. While absolute fixation of the plasma volume cannot occur in the nature of things, the considerations reviewed above indicate only a narrow range for the volume changes which may occur.

SUMMARY

Plasma and total blood volume determinations have been made by the vital red method in a series of thirty cases. The conditions represented in these patients include extremes of total corpuscle content, a very wide range in total blood volumes, and instances of edema and anasarca. It has been shown that in all of these conditions, so long as the hemoglobin is above 30 per cent., there is a constancy of plasma volume comparable to the normal. The significance of this phenom-

31. Lamson, P.: J. Pharmacol. & Exper. Therap. **7**:169, 1915.
32. Henderson, L. J.: Nat. Acad. Sc. **2**: 1916.

enon is great, since it shows that variations in the total blood volume, per kilogram of body weight, depend on the corpuscle content, except in patients with very low hemoglobin values in whom there is also a corresponding reduction of the plasma volume. Thus it happens that in a case of polycythemia with a total corpuscle content of seventy-five trillion there may be the same plasma volume per kilogram as is found in a case of pernicious anemia with a total corpuscle content of three trillion cells. In this connection attention has been called to the universally accepted high figures for blood volume in pernicious anemia and chlorosis, which vary greatly from present known and theoretical considerations.

After acute hemorrhage it has been shown that, ordinarily, rapid dilution of the plasma volume to its former normal level occurs and that it remains constant thereafter, even though the total blood volume may be much reduced by reason of loss of red corpuscles.

Certain exceptions to the general proposition of a constant plasma volume have been cited, such as hemorrhage and shock, edema of the lungs, excessive sweating and diarrhea of severe type, including cholera. Brief mention has also been made of alterations in blood volume incident to changes in altitude.

Emphasis has been placed on the necessity for a normal tissue fluid reserve. When such a reserve is present the blood plasma volume tends to remain at a normal physiologic level.

Finally, a note has been made suggesting a source of error in methods for blood volume determinations that depend on dilutions of whole blood, or primarily upon the corpuscle content. Methods by which the more fixed plasma volume may be directly determined seem to offer the most accurate results.

CONCLUSIONS

1. The constancy of the plasma volume in terms of body weight in health has been demonstrated by previous work and is verified in five cases of the present series. The value is $\frac{1}{19.6}$, or 5.1 per cent. of body weight.

2. The constancy of the plasma volume found in twenty-five cases of widely varying conditions with respect to the circulation, including edema, is a striking fact. The value for this series is $\frac{1}{20}$, or 5 per cent. of the body weight.

3. Variations in the total blood volume per kilogram of body weight are due for the most part to changes in the corpuscle content of the blood.

4. Previous figures quoted in the literature for the blood volume in pernicious anemia and chlorosis are too high.

5. In edema associated with cardiac and renal disease the blood plasma retains its normal value per kilogram of body weight.

6. Recovery after hemorrhage is associated with rapid restoration of plasma to the normal plasma level provided the tissue fluid reserve is adequate. Complete restoration of the total blood volume is dependent on increase in the number of corpuscles. Overdilution of the plasma after hemorrhage has not been encountered.

HEREDITARY HEMORRHAGIC TELANGIECTASIA WITH RECURRING (FAMILIAL) HEREDITARY EPISTAXIS

WITH A REPORT OF ELEVEN CASES IN ONE FAMILY *

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This rare affection of the skin and mucous membranes of the nose and mouth, which may involve also the cheeks, ears, tongue, lips, fingers and other parts of the body, is associated with recurring epistaxis of the familial type. In one of my cases, hemorrhage in the brain occurred, causing temporary hemiplegia and other symptoms of apoplexy. I have been able to find only thirty case reports. Steiner [1] found twenty-eight, including three of his own. Osler, in one of the best contributions to the subject,[2] reported three cases; and at that time (1901) he could find only one reference to a similar case, reported by Rendu.[3] Six years later, Osler [4] reported an additional case. However, he overlooked the cases reported by Chiari [5] and by J. W. Legg.[6] Only eight cases were found by A. Brown Kelly,[7] and he reported two cases of his own. None of the numerous works on dermatology, rhinology or medicine mention this condition. Hartzell [8] speaks of "inherited hemorrhagic telangiectasis," and also makes reference to papers by Hyde,[9] Crocker,[10] Mandelbaum,[11] Osler, Gjessing,[12] Hutchinson,[13] Stokes [14] and Majocchi [15] on telangiectases.

Among the most striking characteristics of this disease is the tendency to affect more than one member of a family, and the marked

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1. Steiner, W. R.: Arch. Int. Med. **19**:194 (Feb. 15) 1917.
2. Osler, W.: Johns Hopkins Hosp. Bull. **12**:333, 1901.
3. Rendu: Gaz. d. Hôp. **49**:1322, 1896.
4. Osler, W.: Johns Hopkins Hosp. Bull. **18**:401, 1907. Id. Quart. J. Med. **1**:53, 1907.
5. Chiari, O.: Erfahrungen auf dem Gebiete der Hals-und-Nasenkrankheiten, Vienna, 1887, p. 60.
6. Legg, J. W.: Lancet **2**:856, 1876.
7. Kelly, A. B.: Glasgow M. J. **65**:411, 1906.
8. Hartzell, M. B.: Diseases of Skin, Ed. 2, J. B. Lippincott Company, Philadelphia, 1919, p. 591.
9. Hyde, J. N.: Brit. J. Dermat. **20**:33, 1908.
10. Crocker: Atlas, pl. 71, Fig. 1.
11. Mandelbaum, W.: Vrtljschr. f. Dermat. u. Syph. **17**:186, 1882.
12. Gjessing, E.: Hospitalstidende **8**:1151, 1915.
13. Hutchison and Oliver: Quart. J. Med. **9**:67, 1916.
14. Stokes, J. H.: Am. J. M. Sc. **149**:669, 1915.
15. Majocchi, D. R.: Acad. delle Science dell Institute di Bologna, 1905.

tendency of a large number of the patient's relatives to suffer from epistaxis for many years. For example, two of Osler's patients were brothers and frequent attacks of epistaxis occurred in five other members of the family. Legg's patient had always shown a tendency to bleed from traumatic causes, and had painful swelling of the joints at regular intervals, resembling the "hemophilic" state. There was a history of epistaxis in three generations, and developmental telangiectases were present on the patient's face and trunk, but there was no history of hemophilia. This was the first family in which telangiectases were found. Babbington [16] reported a case of hereditary epistaxis in a native of Lincolnshire. The patient had been subject to frequent and violent attacks of epistaxis during all her life. She had four children, two of whom (man and woman) likewise had habitual and severe attacks of epistaxis. Recurring epistaxis had been observed for five generations. Rendu [3] was the first to associate the tendency to epistaxis with multiple telangiectases as manifestations of a distinct clinical entity. The condition must not be considered as being hemophilic, nor should it be confounded with the so-called hemorrhagic diathesis, nor with the acquired angiomatous lesions occurring in cirrhosis of the liver.

Hanes [17] described fifteen cases, including cases of his own, occurring in two families. He overlooked Josserand's [17a] and Gottheil's [18] cases. He defines the condition as a hereditary affection, manifesting itself in localized dilatations of capillaries and venules, forming distinct groups or telangiectases, which occur especially on the skin of the face and the nasal and buccal mucous membranes, and give rise to profuse hemorrhage, either spontaneously or as the result of trauma. A hereditary tendency, both as to the formation of telangiectases and epistaxis, is the only factor constantly present. Syphilis, alcohol and other infections or intoxications do not appear to have any definite relation to this condition.

A number of cases have been reported, but with no other instances in any of the patients' families—isolated examples, in other words—of a similar condition, but not of the typical hereditary and familial variety. In some cases telangiectases, of hereditary nature, were noted in one or several members of a family, but without recurring epistaxis; in others, persistent, severe, recurring attacks of epistaxis of familial type were mentioned, but no telangiectases were reported in the patient or any of the members of the family. Such isolated

16. Babbington, B. G.: Lancet **2**:362, 1865.
17. Hanes, F. M.: Johns Hopkins Hosp. Bull. **20**:63, 1909.
17a. Josserand: Bull. Soc. méd. d. hôp. de Lyon **1**:244, 1902.
18. Gottheil, W. S.: Internat. Dermat. Congr. VI, 1907, Tr. **1**:165, 1908.

instances have been reported by A. Brown Kelly,[7] Fox,[19] Vidal,[20] Lack,[21] Galloway,[22] Adamson,[23] Chauffard,[24] Babbington,[16] Lane,[25] Kopp,[26] Hyde,[27] Frick,[28] Létienne and Arnal,[29] Stokes,[14] Osler,[3] Morrow [30] and several others.

Hanes [17] believes that three factors of etiologic import are heredity, repeated traumatisms and the abuse of alcohol, and that the hereditary tendency to the disease is by far the most striking and constant feature.

Males and females are affected alike, and are equally capable of transmitting the disease to their offspring. Hemorrhage is the one constant symptom of the disease and the source of all the other symptoms. Secondary anemia may become quite serious. In the great majority of the cases hemorrhage occurs in the form of epistaxis. In some cases hemorrhage may occur from the telangiectases on the tongue, lips, fingers or buccal mucous membrane, and even rectal bleeding may occur. In my case, the patient had cerebral hemorrhage along with severe attacks of nosebleed, and on two occasions profuse bleeding occurred from the tip of the tongue and the lip.

Multiple telangiectases constitute the sole characteristic of this condition. Most commonly they occur on the buccal and nasal mucous membranes and lips. They have been noted on the face, feet, hands, ears, scalp, neck, forearms and chest. Coe,[31] Chauffard,[24] Chiari [5] and Legg [6] have mistaken these cases for hemophilia.

Pringle,[32] in discussing Sequeira's case,[33] reported a case of telangiectases of the skin associated with hemorrhage from the throat and severe hemoptysis from a large dilated blood vessel on the epiglottis. Phthisis was not present. Nearly all the hereditary cases that I was able to find recorded in the literature have been epitomized by Weber,[34] Hanes,[27] Kelly [7] and Steiner;[1] Stokes [14] reviewed many of the isolated instances, particularly the generalized telangiectasia cases.

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19. Fox, T. C.: Brit. J. Dermat. **20**:145, 1908.
20. Vidal, E.: Bull. et mem. Soc. Med. d. hôp. de Paris **81**:186, 1880.
21. Lack, L.: Proc. Roy. Soc. M., London **2**:109, 1908.
22. Galloway, J.: Proc. Roy. Soc. Med., London **4**:42, 1910.
23. Adamson, H. G. P.: Proc. Roy. Soc. Med., London **1**:44, 1907.
24. Chauffard: Bull. et mém. Soc. méd. de Hôp. de Par. **13**:352, 1896.
25. Lane: J. Heredity **7**:132, 1916.
26. Kopp, K.: Arch. f. Dermat. u. Syph. **38**:69, 1897.
27. Loc. cit., Ref. 9.
28. Frick, W.: J. Cutan. Dis. **30**:334, 1912.
29. Létienne, A., and Arnal, E.: Arch. gén. de méd., May, 1897, p. 513.
30. Morrow, P.: J. Cutan. and G.-U. Dis. **12**:74, 1894.
31. Coe, J. W.: J. A. M. A. **47**:1090 (Oct. 6) 1906.
32. Pringle: Proc. Roy. Soc. Med., London **6**:129, 1912.
33. Sequeira, J. H.: Brit. J. Dermat. **25**:154, 1913.
34. Weber, F. P.: Brit. J. Dermat. **20**:159, 1908. Proc. Roy. Soc. Med., London **1**:44, 1907.

Weber concludes: (1) That the disease affects and is transmitted by both sexes. (2) That the hemorrhage in most cases is only from the nasal mucous membrane; in some cases also from the lesions on the tongue, fingers and cheeks. (3) That in most cases the morbid syndrome is not connected with any hemophilic tendency, or any diminution of blood coagulability. (4) That the cutaneous angiomas usually first attract attention toward middle life. (5) That in most cases a tendency to nose bleeding has been present from early life, or, at all events, many years before cutaneous angiomas were observed. (6) That with advancing years attacks of hemorrhage and the anemia become more severe. The telangiectases are disseminated more or less numerously over the face, lips and ears, and on the mucous membrane of the buccal cavity and nose.

In Osler's third case there were some lesions about the trunk and hands. In Kelly's cases the finger tips were involved, and in one the nail bed, as in Weber's case. In Chauffard's case there was no heredity, and although not truly a hemophiliac, the patient bled easily from the gums, and the least pin prick bled freely. Slight arteriosclerosis was present.

Wilson's [35] case of "eruptive angiomata" occurred in a man, 30 years of age. He had epistaxis and bleeding from the gums. Red "spots" were noted on the face, neck, arms and hands. In Bligh's case [36] bleeding ocurred from the angiomas. Fearnsides [37] reported telangiectases in six children, associated with protracted diarrhea, wasting, edema, purpura and erythema. No other members in the families were affected.

No epistaxis was noted, and no mention is made of hemorrhages (external and free) in the patients or any of their relatives. In these cases the various rashes were the expression of vascular dilatation, particularly telangiectases. The rashes were the result of wasting, due to the protracted diarrhea. Erythema was present in all (six) cases, but purpura was present only in two cases. The patients were one boy aged 3 years, and five girls aged 10, 3, 5 and 9 years, and 17 months respectively.

Adamson's [38] patient was 28 years old, and had telangiectases on both sides of the neck, chest and cheeks. No hemorrhages were noted and no other member in the family was similarly affected.

Sequeira [39] reported the case of a woman, aged 55, who had red "spots" on the face and fingers. She had hemorrhages from one of

35. Wilson, E.: J. Cutan. M. & Dis. Skin **3**:198, 1869.
36. Bligh, W.: Lancet **1**:506, 1907.
37. Fearnsides, E. G.: Brit. J. Dermat. **24**:35, 1912.
38. Adamson, H. G.: Proc. Roy. Soc. M., London **2**:128, 1908.
39. Sequeira, J. H.: Proc. Roy. Soc. Med., London **6**:128, 1912.

the telangiectases. One daughter had epistaxis; no other relative had a similar affection. The spots on the left index finger bled spontaneously several times in the coursse of three or four years. She had attacks of epistaxis nearly every morning for several years. She may have had a chronic renal condition. Hypertension and thickening of the retinal vessels were noted. She had punctate patches on the tongue, cheeks and lips.

Wilson's case [35] is not included in the lists of reported cases by either Steiner or Hanes. In this case copious bleeding from the gums and nose occurred, and later "red papulae with diffuse areola"—angiomas—developed suddenly on the face, neck, hands and arms. Anderson's patient was a house painter, aged 39 years. Angiomas first appeared when the patient was 11 years of age. He had rectal bleeding. Mandelbaum [11] described a case occurring in a man, aged 30 years. He had syphilis at 17. At 21 he developed vascular lesions on the face. Later on they appeared on the neck, limbs and chest. These lesions were disseminated purplish red nodules varying in size from a pinhead to a linseed.

Ullmann [41] reported the case of a woman, aged 40 years, who had roundish purplish angiomas on the face varying in size from a hempseed to a small pea. Later more lesions developed, even on the tracheal and bronchial mucous membrane. Hemoptysis occurred. The patient died from pneumonia. At the necropsy angiomas were found in the skin, respiratory mucous membrane, rectum, urethra and liver. This case is not of the hereditary type, as no mention is made as to any of the patient's relatives being similarly affected or as suffering from epistaxis.

Chauffard's patient [24] was a woman, aged 50 years. She had very frequent attacks of epistaxis. Many telangiectases were present on cheeks, forehead, ears, septum of nose, lower lip and tip of tongue. Secondary anemia was found. Heredity could not be established.

Vidal [20] recorded the case of a woman, aged 31 years, who had telangiectases on the breast, neck, wrists, forearms, thighs, feet, back of hands, back and abdomen. She sometimes had a little nosebleed. No similar condition was noted in any other member of the family.

Létienne and Arnal [29] reported a case occurring in a woman, aged 27 years. She developed punctiform vascular dilatations.

Shield [42] reported a case in which there was a portwine nevus of both hands and feet, with spots on the extremities and the face and chin.

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40. Anderson, W.: Brit. J. Dermat. **10**:114, 1898.
41. Ullman, C.: Arch. f. Dermat. u. Syph. **35**: 1896.
42. Shield: Brit. J. Dermat. **19**: (July) 1907.

Crocker [10] reported a case in a girl, 7 years of age, with an enormous number of dilated vessels, beginning at 5 years of age, and occurring on the face, back of forearm and hand.

Telangiectases, symptomatic of disturbance of the general circulation are not infrequent, either when the heart itself is at fault, or when some distal portion is involved, sometimes by disease of the lungs, spleen, liver or thyroid. In exophthalmic goiter the circulation may be disturbed considerably and telangiectasis may form.

Kennan [43] reported two cases (a boy and a girl) of multiple telangiectases associated with recurring epistaxis, occurring in twins, aged 10 years. The telangiectases on the face of both children were first noticed four years before, following an attack of measles. The boy's nose bled frequently. Only a few "spots" were present on the mucous membranes in both cases. The father of the children bled occasionally from the nose. He has three brothers. Each one bleeds frequently from the nose, but a sister has never had epistaxis. A girl aged 14 years, has frequent epistaxis. Another girl, aged 12 years, has occasional nosebleed. In none of these cases has bleeding occurred from anywhere except the nose. There was no history of the occurrence of telangiectases in any of them, except in the two children (twins).

Lack [21] reported a case of telangiectases with epistaxis in a woman, 53 years old. She suffered from epistaxis for thirty years. At times bleeding was profuse, and always from the anterior part of the septum on the right side. She had typical nevoid spots on the right cheek, lips, tongue, palate and chest. The patient thought that these lesions sometimes disappear. There was no history of a tendency to bleed in other ways; no history of similar disease in other members of the family. The patient had seven children, and brothers and sisters, but all were well.

Galloway,[22] reported a case of multiple cutaneous telangiectases of recent origin, in a man 35 years of age. The patient had had repeated attacks of malaria. He was tuberculous. The sputum contained tubercle bacilli. Blood clotting time was normal. Red spots developed "ten months ago," mainly on the face, neck and shoulders, some on the arms and legs. They were "spider" telangiectases, "spider or stellate-angiomas." The liver was enlarged. The lesions bled profusely when traumatized. No telangiectases were seen on the mucous membrane of the buccal cavity, nasopharynx or larynx. The patient was not hemophilic. No history was obtainable of a similar condition in any other member of his family. This case resembles the hereditary type, but it is probably a case of the type appearing rapidly in certain

43. Kennan, R. H.: Med. Press & Circ. **33**:458, 1902.

patients with cirrhosis of the liver. Electrolysis and carbon dioxid snow was tried satisfactorily in this case.

Kopp [44] reported the case of a young man, aged 19 years, who eighteen months before noticed some small red angiomas over the scrotum and legs, and later on the trunk and arms. No history of a similar condition in any other member of the family was obtained.

Hutchison and Oliver [43] reported three cases in which frequent attacks of epistaxis had occurred since early years, with a definite history of nosebleed in other members of the family. Two of the patients showed multiple telangiectases of the face, with lesions on the buccal mucous membrane.

Case 1.—A carman, aged 49 years, widower, had attacks of epistaxis all his life; sometimes bled from the lips, gums, ears and rectum. Red spots were present on the nose, cheeks, ears, lips, and a few on the fingers; several punctate lesions were noted on the septum of nose. There was secondary anemia, 3,250,000 erythrocytes. Blood Wassermann was negative. The lesions in the nose were cauterized without checking the epistaxis. Calcium lactate, 15 grains, three times daily, did no good. Diathermy applied to the lesions on the lip was effectual.

Case 2.—The father of the first patient, aged 77 years, had frequent attacks of bleeding since childhood, with occasional bleeding from the rectum and gums. He had had spots on the face for years. Telangiectases were present on both ears and cheeks, and on the inside of the nose. They were numerous on the tip of the tongue. A few lesions were present on the lips. There was secondary anemia. Patient denied venereal disease.

Case 3.—John G., aged 25 years, a son of the first patient, had epistaxis for a long time. There was no history of chilblains. He denied venereal disease. There were some miliary red spots on the tip of the tongue and the mucous membrane of the lips; a few were present on the right shoulder and there were two raised pinkish lesions on the right cheek.

Morrow [20] reported an unusual case of telangiectases, occurring in a girl, aged 10 years. When 5 months old she had frequent convulsions. During the course of these seizures patches of telangiectases developed on the face and body. Spots were noted on the left cheek, chin, face, nose and malar regions. She was a weakminded child. No mention is made of epistaxis, or of any similar condition in any other member of the family.

Hanes [17] reported recurring hemorrhages in four generations of one family. Multiple telangiectases of the skin and mucous membranes were noted on the gums, tongue, face, fingers, under the nails, and on the right lower eyelid. The patient was a woman, 53 years old. She was subject to severe nosebleed for three years. Her mother died at 48, from heart disease and dropsy, and she, too, had severe epistaxis all her life. Her mother also had red spots on the face and lips, and in the mouth. The patient's two brothers had epi-

44. Kopp, K.: Arch. f. Dermat. u. Syph. **38**: (Jan.) 1897.

staxis all their lives and both exhibited typical red spots on the face and lips.

The patient had secondary anemia of a severe type (erythrocytes, 1,500,000; hemoglobin, 15 per cent.). Her son, aged 33 years, was not subject to recurring epistaxis, but had severe hemorrhages from telangiectases on the lips and tongue, and from under the nail on the left middle finger. He occasionally bleeds from the nose. Hanes also reports the case of the other son, aged 32 years, and of a daughter, aged 18 years. He describes another family, with recurring epistaxis in sisters, and multiple telangiectases affecting chiefly the mucous membranes. No symptoms of hemophilia were present in any of these cases. The three sisters were aged 46, 26 and 28 years, respectively, and two brothers were aged 34 and 38 years, respectively. The two brothers both have nosebleeds, but neither has telangiectases. On searching the literature Hanes found thirteen other families recorded. He mentions those of Babbington,[10] Legg,[6] Chiari,[5] Chauffard,[24] Rendu,[3] Osler,[2] Osler,[4] Kelly [7] Ballantyne,[45] Hawthorne,[46] Weber,[47] Phillips [48] and Waggett.[49] As treatment, he advises the destruction of the telangiectasias by the use of the chronic acid bead, followed by an alkali. Repeated cauterizations may be necessary within the nose.

Létienne and Arnal [29] reported the case of a woman, aged 27 years, suffering from exophthalmic goiter, who had a shower of telangiectases over the sternum, and over the remainder of the body. They disappeared on pressure. The macular lesions were round and oval in shape, scarlet to dark red in color, and of variable size. The shoulders and neck were free.

Hyde [27] reported four cases.

Case 1.—A woman, aged 57 years, had symmetrically placed telangiectatic macules on the cheeks, more conspicuously displayed on the left side. The lesions varied in size from a small pinhead to half a split pea. There was one spot over the left sternoclavicular articulation. There was no history of epistaxis, or a similar condition in any other relative.

Case 2.—A widow, aged 50 years, had a lesion on the right side of the brow, and a small lesion on the left cheek which disappeared on firm pressure. On the right cheek were dull purplish-red puncta, disappearing on pressure. There were a few scattered papules on the scalp. The urine contained renal casts and albumin. The heart was hypertrophied.

Case 3.—A woman, aged 43 years, had one typical vascular lesion on the upper lip. A few small telangiectases were present on the upper part of the chest and there were some distended capillaries on the cheeks.

Case 4.—A young woman, aged 24, had diffuse redness over the forehead and cheeks.

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45. Ballantyne, A. J.: J. Glasgow M. J. **70**:256, 1908.
46. Hawthorne, C. O.: Lancet **1**:90, 1906.
47. Weber, F. P.: Lancet **2**:160, 1907.
48. Phillips, S.: Proc. Roy. Soc. Med., London **1**:64, 1908.
49. Waggett, E. B.: Proc. Roy. Soc. Med., London **1**:70, 1908.

Wise [50] reported a case of infective angioma of Hutchinson or angioma serpiginosum. Hutchinson, Crocker and Dore reported a case by Pringle.[32] Two cases were reported by Howard Fox in 1911. The patients were also examined by Wise.[50]

Frick [28] reported an unusual case of dilated capillaries in a man, 50 years of age, a landscape gardener, expressman and laborer. The skin trouble began fifteen years before on the nose, then appeared on the cheeks, neck and forehead. He never used alcoholics or tobacco. The backs of the fingers were also involved. The mucous membranes of the mouth and nose also contained dilated capillaries. No mention is made of epistaxis. Blood coagulability was normal. The patient committed suicide.

Terrell [51] reported a case of acquired general capillary telangiectases in a woman, 47 years old. Bright red discoloration of the skin on the back of her wrist was due to a dilatation of the capillaries. The trouble began when she was 32 years of age. It first appeared in small patches on the outer edge of the feet, then on the wrists and both forearms, extending up almost to the elbows. The extensor surfaces of the extremities were principally involved. Epistaxis was not mentioned. There was no history of similar trouble in any other member of the family. She had two children, who apparently were well.

Babbington [16] reported a family having recurring epistaxis. No mention is made, however, of multiple hereditary recurring telangiectases, and therefore, I hesitate to accept these as typical. The male patient (son of the woman whose case was reported by Babbington) died of the disease. The female patient (a sister of the man) had six girls, three of whom suffered from nosebleed during the earlier period of their lives. Other members of the family and their children have had habitual severe epistaxis—observed in five consecutive generations and for the last three generations in two branches.

Richardson [52] reported cases of familial epistaxis. A man, 53 years old, a teamster, gave no history of venereal disease. Spots were noticed on the face ten years or more ago. Numerous telangiectases were present on the face, about the mouth, nostrils and chin, and a few were seen on the septum of the nose. The trunk and lower extremities were clear. The coagulation time was normal. A secondary anemia was present: erythrocytes 3,400,000; hemoglobin, 55 per cent. The blood Wassermann was negative. Patient suffered from epistaxis. Of five children, two died in infancy. A daughter of the

50. Wise, F.: J. Cutan. Dis. **31**:725, 1913.
51. Terrell, W. H.: Indiana M. J. **15**:8, 1896.
52. Richardson, H. B.: Am. J. M. Sc. **154**:95, 1917.

old lady (sister of the patient) is well, except that she also was subject to bleeding from the nose, although less severe than that of the patient. A son (brother of the patient) was living and well. The mother died of an operation during childbirth.

The sister and brother of patient each had a daughter, of whom nothing is known as to epistaxis or spots. A maternal cousin had spots on the face and was subject to epistaxis. Her two sons and two daughters were subject to epistaxis. The patient's younger son, aged 25 years, traveling salesman, denied venereal disease. He had had epistaxis frequently ever since he could remember, three times a week. He had telangiectases on the cheeks, nose, ears and the tip of the tongue, and a few on his fingers. Rhinoscopy disclosed no telangiactases. He never bled freely from cuts. On the left side of the nose were two minute threadlike telangiectases of a radial arrangement. On the cheeks, there was a slight telangiectatic enlargement of the finer vessels which disappeared on pressure. Similar lesions were present. He had a minute angioma on the right upper arm.

Legg's patient was a man, aged 65 years. He had suffered from attacks of epistaxis since boyhood. One sister was subject to nosebleed. One son and one daughter suffered from nasal hemorrhages. The patient had numerous small nevi all over the face, forehead and trunk. They were not congenital and were first noticed when he was 40 years of age. The patient had joint pains and a tendency to traumatic hemorrhages. Legg thought the condition was due to congenital weakness of the vessels, which remained permanently in a stage of early formation.

Van Wagenen [53] reported the case of a woman, aged 32 years, a native of Russian Poland. Her mother had suffered from epistaxis since early childhood. Two brothers, aged 27 and 21 years, respectively, suffered from nosebleed since childhood but never had any hemorrhages from any other part of the body. They had spots on the tongue, nasal septum, face and arms. The patient had bleeding from the tongue and nose for some time. There was no swelling of the lower extremities. She had had no severe hemorrhages from slight wounds. Blood coagulation time was normal. The erythrocytes numbered 3,600,000; hemoglobin, 80 per cent. The Wassermann was negative. Van Wegenen used thrombokinase to check the bleeding, and administered calcium chlorid or calcium lactate. Cauterization had been tried. Injection of hot water into the base of the lesions on the tongue was suggested by him.

Gundrum [54] reported four cases of the disease in the same family.

53. Van Wagenen, C. D.: Med. Rec. **109**:81, 1912.
54. Gundrum, F. F.: California State J. M. **17**:78, 1919.

CASE 1.—Lucy M. had ten telangiectases on the tongue, from 0.5 to 3.5 mm. in diameter. She had severe nosebleeds. Two telangiectases were noted on the nasal septum.

CASE 2.—The mother of the first patient, aged 44 years, had spots on her cheeks, ears, eyelids and nose. She had five telangiectases on the septum of the nose, and suffered from severe attacks of epistaxis.

CASE 3.—Brother to Lucy M., aged 47 years, had twenty spots on his face and nose. He did not have much trouble with nasal hemorrhages.

CASE 4.—Grandmother of Lucy M., was aged 65 years at the time of her death. She had thirty spots on the face and suffered from severe epistaxis. Treatment consisted of cauterization of all telangiectatic lesions with chromic acid bead, heat or other means to "destroy the tiny mass of dilated blood vessels.

Coe [21] reported the case of a physician, aged 53 years, as a "hemophiliac" (erroneously), but the case was one of hereditary telangiectasia with familial recurring epistaxis, and is, therefore, included in this paper as an example of the clinical entity here discussed. The case is further described by Osler [4] and is reported as his fourth case of this condition. Coe reports four other cases of true hemophilia.

Osler's first case [2] occurred in a seaman, aged 57 years. The mother never had epistaxis. A sister died at 59, of Bright's disease. She had had epistaxis since childhood. Another sister bled from the nose and mouth. The patient reported, had one child, aged 13 years, who bled from the nose. A grand niece, granddaughter of the patient's eldest sister, also had epistaxis. The patient had syphilis when 27 years old. He had secondary anemia; erythrocytes, 2,980,000; hemoglobin from 15 to 20 per cent. Coagulation time was from five to seven minutes (Wright's). A number of telangiectases were noted on the tip and edge of the tongue.

The patient's brother, Wm. B., aged 55 years—had "spider" angiomas on the nasal septum, lips and side of the nose, on the cheeks and on the ears. He had erythrocytes, 4,488,000; hemoglobin, 71 per cent. Coagulation time was four minutes. He took calcium chlorid, 15 grains, three times daily. The second patient had cancer of the stomach, liver, lungs and brain. Seven members of his family have been subject to epistaxis.

Osler's third case is not altogether typical of the disease under discussion, because it seems to be an isolated instance not of the true family type, but of the kind that is associated with cancer of the liver and other organic disease, such as syphilis, nephritis, gallbladder trouble, scleroderma, cardiorenal disease, etc. Osler's third case occurred in a man, aged 49 years, who had had epistaxis since childhood. There were no bleeders in the family, and none had serious attacks of epistaxis. He denied syphilis. He had a secondary anemia; erythrocytes, 3,460,000; hemoglobin, 38 per cent.

Telangiectases were present on the face, lips, tongue and scalp. His attacks of epistaxis began at the age of 10. He bled also from the telangiectatic lesions in the gums and lips.

Osler's fourth case [4] occurred in a physician, aged 53. He had numerous telangiectases of the skin of his face, ears and lips, and secondary anemia. He had been a nosebleeder for many years. He also bled from the "spots." The bleeding began at his tenth year. His grandfather, father and one sister had had "spots" and had bled in the same way. His son had epistaxis but no "spots." The patient did not have joint trouble. There was no severe bleeding from the cuts.

Scattering angiomas (telangiectases) of the skin are frequently found in apparently normal persons and have no pathologic significance. However, they may develop in large numbers in varying sizes on the skin of persons with diseases of the pancreas and liver, cancer, chronic jaundice from gallstones, or simple catarrhal jaundice, also in tertiary syphilis and as a result of exposure of the skin to the roentgen ray. In Osler's second case telangiectatic lesions were present in the mucous membrane of the stomach. The patient died from general carcinomatosis.

Rendu [3] reported a case in a man, aged 52, who suffered from repeated attacks of epistaxis. He had small superficial angiomas of the skin of the face, neck and thorax, and in the mucous membrane of the mouth. The patient's mother and brother had repeated attacks of epistaxis. His father died of dysentery, with repeated crises of melena, at the age of 55. He had a few scattered lesions over the neck and chest. Rendu used for the epistaxis, antipyrin, 50 gm.; tannin, 1 gm. and sugar 10 gm. As stated, Rendu was the first to describe this condition as a distinct clinical entity.

Fox [10] reported the case of a young woman, Emily B., who had epistaxis at 10 years of age; at 14 "spots" appeared in the left lower axillary region and left side of the back; later they appeared also in the right lower axillary region and lower part of the chest, becoming bilateral. She had marked epistaxis, and recently began to have bleeding from the rectum. Sigmoidoscopy showed that the lower bowel was normal. A family history of bleeding of epistaxis could not be obtained.

Kelly's [7] patient, aged 41 years, had suffered from severe recurring epistaxis. Her father died at 62 from the effects of frequent nasal hemorrhages. Her sister bled from the lips, mouth and nose and had multiple telangiectases on the face and hands and on the mucous membranes of the nose and mouth. There were few lesions on the scalp. The patient's daughter bleeds from the nose and has

red spots on the face. The patient died from a severe and persistent attack of epistaxis (syncope). In this case, there was a history of severe recurring epistaxis with multiple telangiectases of the skin and mucous membranes in the family for three generations.

Morrow,[30] Lanceplaine,[55] Hyde,[27] Kopp,[44] Tanturri,[56] Terrell,[51] Levi and Le Noble,[57] Brocq,[69] Mosny and Malloizel,[58] Gaucher and Crouzon,[59] Létienne and Arnal[29] have reported cases of telangiectasia of the more or less generalized type which were so carefully and thoroughly studied by Stokes.[14] Stokes says, that out of thirty-three cases which he found in his search, he noted that syphilis, plumbism, hyperthyroidism or nephritis was present in twenty-two and possibly in twenty-three.

In Gastou's[60] two cases syphilis was a factor. The father developed telangiectases; the daughter developed localized telangiectasia in early life. There is probably a preponderance of females over males in connection with the development of generalized and localized telangiectasia.

Mandelbaum's case[11] was an old syphilitic with macular, arborescent and nodular telangiectatic and angiomatous lesions, generalized over a considerable portion of the body.

Ehrmann's case[61] occurred in a patient with general arteriosclerosis. He had telangiectases over the trunk and on the extremities. This may have been a case of syphilis.

Stokes[14] reported a case in a widow, aged 34. There was no history of familial epistaxis, hemophilia or telangiectasia in any other member of the family. At 9 years of age she began to suffer from nosebleed. The hemorrhages were severe. This recurring epistaxis ceased abruptly with her first menstruation at 12, and did not recur. Skin trouble began at 29 years. She had had a small telangiectatic lesion below the right eye for many years, and several small pink spots on the dorsum of the feet. Then the wrists, arms, legs, and, lastly, the trunk became involved. There were no lesions on the palms of the hands nor on the face at any time. The scalp, neck and shoulders were free. The configuration of the dilated venules was arborescent, stellate, or lacelike on the legs—arborescent telangiectatic figures. The mucous membranes were negative. The urine was negative. Blood coagulation time was normal. The blood Wassermann was negative

55. Lanceplaine, R.: Thésé de Par., 1904.
56. Tanturri, V.: Ann. de dermat. et syph., 1880, p. 338.
57. Levi and Le Noble: Presse méd., 1896, p. 310.
58. Mosny and Malloizel: Bull. soc. méd. d. hôp. de Par., 1905, p. 847.
59. Gaucher and Crouzon: Ann. de dermat. et syph., 1902, p. 52.
60. Gastou, P.: Bull. Soc. de Dermat. **5**:71, 1894.
61. Ehrmann, S.: Wien. klin. med. Wchnschr. **57**:778, 1907.

once and positive once. The erythrocytes numbered 5,580,000. He reports the case, with a review of other recorded cases, under the title "Generalized Telangiectasia in Association with Syphilis, with Peripheral Vascular Sclerosis."

Head [62] reported two cases of multiple hemangiomas of the skin associated with dyspituitarism.

CASE 1.—A Swedish farmer, single, aged 28 years, gave no history of venereal disease. He had been sick since 8 years of age. The telangiectases appeared when he was 14 on the penis and scrotum, later on the thighs, arms, back and abdomen. No lesions were seen on the mucous membrane of the lips, mouth or nose. There were some telangiectases on the face and neck varying in size from pin-point to 2 mm. in diameter. The Wassermann test was negative; no glycosuria; no epistaxis; pains in the toes and fingers and dull aches in the knees. Four brothers and three sisters are well. Mother died of apoplexy.

CASE 2.—A man, aged 60 years, laborer, with no history of venereal disease or nosebleed, had hemangiomas of the skin of the scrotum and the mucous membrane of the cheeks and lips. He was acromegalic and had mitral endocarditis. Family history was negative. Father and brother died of tuberculosis. The Wassermann test was negative.

Trawinski [63] suggested the name perivasculitis syphilitica telangiectatica for his case. His patient was a syphilitic, and showed macular, arborescent, and striate telangiectases, with gummatous infiltrates in the skin. Frick's patient [28] showed generalized telangiectasia, with carcinoma of the liver with metastases. Wise's case [50] was one of angioma serpiginosum and was studied by Pollitzer. Fox's case [19] showed grouped papular lesions on the trunk, associated with epistaxis in childhood and rectal hemorrhages.

Some of these cases may present features resembling Majocchi's purpura annularis telangiectodes. Majocchi [14] believes that there is some direct action of some toxin on the vessels which excites endothelial reaction and proliferation and brings about this condition. Cardiovascular degenerative conditions (syphilis being the most important) appear to have some etiologic relationship in a few of the reported cases of telangiectasia. Lead, alcohol, hyperthyroidism, dyspituitarism, many of the infectious diseases particularly syphilis, may have some etiological relationship in some cases. This phase of the subject needs further study and investigation.

In Chiari's two cases [5] (two sisters) a history of epistaxis in four generations was obtained, with multiple telangiectases on the skin and mucous membranes, and the condition was erroneously diagnosed as hemophilia. The grandmother and two brothers of the girls suffered from childhood with frequent and severe attacks of epistaxis.

62. Head, G. D.: Arch. Int. Med. **20**:24 (July) 1917.
63. Trawinski, H.: Monatsh. f. prakt. Dermat. **1**:45, 1910.

Kelly's two patients [7] were also sisters. Their mother, two brothers and one sister all suffered from severe nasal hemorrhages. Apparently the sister recovered from these attacks and only bled a little from the nose at the time of the menstrual periods. The two patients reported by Chiari bled from the nose since childhood and one of them also bled from the gums. Both sisters had telangiectases on the face and trunk and on the mucous membranes of the nose, tongue and lips. Their children also suffered from nosebleeding.

The other family reported by Chiari gave a history of severe epistaxis in three generations. Three members of the family suffered with severe attacks of nosebleed from childhood. They had multiple telangiectases on the skin and mucous membranes. When first seen by Chiari, one of them, a young woman aged 30, exhibited telangiectases on the skin and mucous membranes of the nose, tongue and lips. Her father and paternal aunt had the same trouble. Her sister and all her sister's children were similarly affected, and one of the children died from a severe nasal hemorrhage.

Josserand's [17] patient was a woman, aged 56 years, who had suffered from epistaxis since childhood. Lately she also bled from the lips, gums and tongue. She exhibited telangiectatic lesions on her neck, chest, back and arms, but in greater numbers on the face, lips, tongue and palate. One brother had nosebleed and telangiectases; another brother and her father had been subject to frequent attacks of epistaxis.

Hawthorne's patient [46] was 49 years of age. She had had nosebleed since childhood. There was a history of epistaxis with telangiectases in three generations. The patient's father and sister, and her nine children had frequent attacks of epistaxis. She had telangiectases on her fingers and face. Her father and sister had telangiectases on the face.

Weber's [47] patient was a woman, aged 60, who first noticed telangiectases on her face when she was 42. She had nosebleed and "spots" on her face, ears, lips, tongue, conjunctiva of all the eyelids, the mouth and nose. She also had some lesions on the fingers and under the nails. A daughter, aged 10 years, had frequent nosebleed but no "spots." This family gave a history of recurring epistaxis in four generations. The patient's mother had nosebleed and several "spots" only on the face. The patient had small angiomas on the posterior wall of the pharynx, in the nostrils and on the anterior surface of the epiglottis. Calcium lactate did not stop the epistaxis. Epinephrin was applied locally, and iron and arsenic were given internally.

Phillips' [48] patient was a married woman, aged 56, who had had nosebleed and hemorrhages from the mouth since childhood. Her

father suffered from violent epistaxis and hemorrhages from the tongue. Her sister died from hemorrhages of the gums. The patient had one daughter who had vascular lesions on the tongue and suffered from epistaxis. There was a small red patch on the tip of the tongue, which bled at times. The patient had telangiectases on the mucous membrane of the tongue, nose and mouth.

Waggett's patient,[49] 53 years of age, had hemorrhages from the nose for thirty-three years. He also bled from telangiectases on his face and lips. Telangiectases were also present on the mucous membranes of the tongue and nose. A sister was similarly affected.

Hulke [64] described a case of general telangiectases affecting chiefly the left half of the body. The condition began with the presence of a few nevoid spots in early infancy. Epistaxis is not mentioned, nor was heredity a factor.

Harris [65] reported a case of severe epistaxis, but the patient was suffering from hemophilia. Bligh's case of bleeding telangiectases [36] occurred in a man, aged 32 years, who had nevoid growths and hemorrhages, but gave no familial history. Smith [66] had a patient, a woman, 50 years of age, with multiple venous angiomas on the face and upper part of the trunk.

Ballantyne [45] reported three cases of multiple telangiectases in one family (Hollanders; Zaandam). Red "spots" were present on the palpebral conjunctiva in two and on the lips and other portions of the skin and on the mucous membranes. Several of the patients were subject to nosebleed. The man was 63, his wife 56; a healthy son, 30. A daughter, aged 26, had red spots on the face and one finger. Five of the six members of the family who were examined had telangiectases. One of the boys had spots on the inner surface of the lower lip and tip of the nose and end of his tongue. One boy had no spots, but bled from the nose.

Audry's case was a patient aged 70 years, who had nosebleed for many years. He presented numerous telangiectases on the face, tongue, palate, arms and body. His mother, a great uncle, a great aunt, two sons, five brothers and sisters were all similarly affected. His mother bled from the nose and exhibited telangiectases.

Langmead [67] reported a case of hereditary multiple telangiectases in a man, aged 68 years. There were thirty small vascular red or purplish nevoid lesions on the face. Some had the "spider" form. The lower lip and under surface of the tip of the tongue were involved.

64. Hulke: Roy. Med. Chir. Soc., Dec. 12, 1876.
65. Harris, T. J.: Laryngoscope **28**:890, 1918.
66. Smith, F. J.: Tr. M. Soc. London **21**:358, 1898.
67. Langmead: Proc. Roy. Soc. Med., London **3**:109, 1909.

No telangiectases were seen in the nose. For twenty years the patient bled from the nose. He was first seen by Langmead in June, 1909. He had a secondary anemia. The erythrocytes numbered 2,200,000; hemoglobin, 30 per cent. Four brothers and one sister were subject to epistaxis and exhibited telangiectases. The patient's father was similarly affected. His mother suffered from severe epistaxis only. The patient had two sons, one of whom, aged 35 years, had nevoid patches and epistaxis; the other younger son only bled from the nose. A daughter of one of his brothers had similar patches and was subject to recurring epistaxis. Telangiectases were present in eight members of this family for three generations, and nasal hemorrhage was a symptom in eleven members of the family.

Gottheil's patient [18] was a man, aged 40 years, who bled from his nose, tongue and lips as long as he could remember. His mother had spots on her lips and died, probably as a result of hemorrhages. Two of the patient's children, one sister and three brothers had nosebleed.

Laffont's patient [68] was a woman, aged 48 years, who noticed at the age of 39 or 40 that telangiectases were appearing on the scalp, face, ear, breast and back. Some had disappeared spontaneously. Since puberty she had repeated attacks of nosebleed. Her mother, at 62, had spots on her ears, neck, chest and arm; no mention is made of epistaxis. Her sister had telangiectases on her ears, back of the neck and arm, but no epistaxis. Other members of the family were similarly affected.

Gjessing [12] gives the history of a family in which epistaxis and telangiectases were observed for four generations; one member of the family had endocarditis and hemorrhagic retinitis. The patient whose case is reported, was a man, aged 51 years, who had had severe epistaxis since childhood. When about 25 or 30, he noticed telangiectases on his face and the mucous membrane of his mouth. Next they appeared on the ears, under the chin, on the neck, nose, tongue, hard palate and the right lower eyelid, a few spots developing on several fingers and the left arm. He has bled from the nose and the spots on the cheeks, eyelid and tongue. Two children have bled from the nose. The hemoglobin percentage was 25. Several other members in the family were similarly affected.

Hanes' [17] and Steiner's [1] cases are described so well that I will not repeat the reports in detail. Hanes reported two families with recurring hemorrhages in four generations of one family, and multiple telangiectases of the skin and mucous membranes, but no symptoms of hemophilia. One woman, aged 53, had bled since childhood. Telangi-

68. Laffont: Presse méd. **17**:763, 1909.

ectatic spots were present on the face, lips, tongue, ears, hard palate, gums and the nasal mucous membrane. In the other family four sisters had epistaxis and multiple telangiectases, affecting chiefly the mucous membranes, but no symptoms of hemophilia. A second patient, aged 46, suffered from severe nosebleed throughout childhood. She had telangiectases under the eyes, on the conjunctivae, on the lips, tongue, hard and soft palate and nasal mucous membrane.

Steiner reported three families with this condition.

Case 1.—Family F. G. Recurring hemorrhages occurred in five generations and twenty-one members of this family; telangiectases were observed in five. The patient was a well developed man, 42 years of age, who was admitted to the hospital because of weakness, shortness of breath and frequent nosebleed. He began to suffer from epistaxis at 14. At 16, he had small hemorrhages from a red spot on the face. He denied venereal disease. Angiomas were seen on both cheeks, varying in size from pin-point to 3 or 4 mm. in diameter. Several were present on the nose, tongue, lower lip and ear. There were a few angiomas on the septum of the nose and on the left inferior turbinate. Hemoglobin percentage was 60; erythrocytes numbered 4,696,000; leukocytes 4,800. The patient was given iron and arsenic The spots in the nose were cauterized on two occasions. The Wassermann and luetin tests were negative. The patient's father, grandfather and one aunt, all of whom are now dead, several of his children and grandchildren were similarly affected.

Case 3.—Mrs. A. T., aged 33, bled from the nose, tongue, pharynx and hard palate. These hemorrhages seemed to have been controlled by ergot given internally and locally by tincture of ferric chlorid.

Case 4.—Mrs. D. E., aged 25 years, bled from the nose for nine years, and then began to bleed from the tongue. Both these women (Cases 3 and 4), members of the same family, had angiomatous lesions on the face, tongue, etc.

Case 5.—Family E. M. Recurring epistaxis occurred in three members of the family for two generations; telangiectases with recurring nasal hemorrhages were present in only one member of the family. This woman was 41 years of age. She began to have epistaxis when 25 years of age. Her gums bled easily. Eight or nine years ago she began to have red spots on her cheeks, then on the hands and wrists. She was very anemic. Erythrocytes, 2,560,000; hemoglobin, 55 per cent. (Dare); coagulation time, 4½ minutes. One sister was subject to nosebleed all her life. Another sister had a son who bled from the nose. No mention is made as to the presence of telangiectasia in any other member of the family.

Case 6.—Family C. L. Man, aged 62 years, bled from the nose occasionally since childhood. He was a well nourished Italian. The Wassermann test was negative. Telangiectases were noted on the forehead, cheeks and nose; pinpoint, nodular and spider forms. There was a history of epistaxis and telangiectases in this family for three generations. The patient's father died at 92; he too had telangiectases and nasal hemorrhages. Of the patient's six children, only a daughter suffers from occasional attacks of nosebleed.

REPORT OF AUTHOR'S CASES

Case 1.—Mrs. R. W., aged 42 years, white, married, has had severe persistent and recurring attacks of epistaxis since childhood. She has two daughters and two sons. One daughter, aged 20 years, has bled from early childhood. The other daughter, aged 11 years, has bled from the nose nearly all her life. The patient has telangiectatic lesions on the nose, nasal septum,

lips, tongue, chin and cheek. There are a few lesions on the left side of the neck, and one on the middle finger of the left hand. None are seen on the thighs and legs. The larger spots on the tip of the tongue have bled on several occasions. Bleeding from lower lip occurred on one occasion. Sometimes the hemorrhages from the nose are very profuse and uncontrollable. The patient received ferrous carbonate, sodium arsenate, calcium lactate and calcium chlorid at various times. She also used thyroid and lutein for a brief period. Secondary anemia is present. Her eldest daughter has a few spots on the tongue and one over the right clavicle and some on the forearms. The younger daughter has none on the face or body, and only two very small ones are seen on the tongue. The patient's mother, who is dead, also had recurring attacks of epistaxis and red spots. Three sisters are married. Two sisters have nosebleed; one sister, 34 years of age, bleeds profusely from the nose.

Her four children, J. H., 13; A. H., 11; M. H., 6, and I. H., 3; all suffer from epistaxis. Another sister, A. L., aged 32, bleeds from the nose. Her son, M. L., aged 8, does not bleed. A third sister, Mrs. M. C., aged 30, and two children, J. C., aged 10 and E. C., aged 5, apparently do not bleed.

Mrs. R. W. (the oldest daughter), had a "stroke" and hemiplegia Jan. 20, 1918, after a little giddy spell. This attack was due to defects in the small vessels, like those occurring in other parts of the body, or a peripheral sclerosis. Blood Wassermann tests were negative on several occasions. Blood chemical tests showed urea nitrogen 18 mg. in 100 c.c. of blood; nonprotein nitrogen, 35 mg.; creatinin, 2.20 mg.

Urine.—Jan. 26, 1918: Trace of albumin; sugar less than 0.1 per cent.; chlorids, 0.5 per cent.; specific gravity, 1.005; granular and hyalin casts; flat and round and caudate epithelial cells; urea, 1 per cent.; acid.

March 11, 1919: Albumin present; urea, 0.5 per cent.; amorphous urates present; total solids, 16.3 gm.; faintly acid; specific gravity, 1.009; no casts; no sugar;.

July 24: Acid; specific gravity, 1.015; no acetone; no diacetic acid; slight excess of indican fifteen times normal; urea, 0.6 per cent.; no diazo reaction; slight excess of urorosein; no casts and no cylindroids; many red blood cells; many renal epithelial cells; large number of leukocytes (pus). Thirty-five ounces of urine were voided in twelve hours.

Eyes: April 30, 1919. Posterior polar cataracts in both eyes.

Blood: Coagulation and bleeding time normal. Feb. 15, 1918. Erythrocytes, 3,980,000; leukocytes, 12,600; hemoglobin, 61 per cent. Differential count: polymorphonuclears, 64 per cent.; small mononuclears, 26 per cent.; large mononuclears, 4 per cent.; transitionals, 2 per cent.; eosinophils, 3 per cent.; mast cells, 1 per cent. July 24, 1919. Erythrocytes, 300,000; leukocytes, 14,600; hemoglobin, 68 per cent.; polymorphonuclears, 60 per cent.; large mononuclears, 12 per cent.; small mononuclears, 24 per cent.; transitionals, 2 per cent.; eosinophils, 2 per cent.

The phenolsulphonephthalein renal function test was practically normal. The blood pressure varied during the past three years between 128 systolic, and 90 diastolic, and 110 systolic and 80 diastolic.

Comment.—At the time she had the stroke it was difficult to decide as to the cause. One could not easily differentiate between embolism, thrombosis and hemorrhage. There was no evident source of an embolus. A faint murmur could be heard over the heart, and at times it was faintly audible at the apex, but it could be attributed to the anemia. Shortly after the cerebral hemorrhage, the systolic blood pressure was 140; however, at no time during the past three years has it been higher than the normal average, often below. She complains of a heavy feeling and numbness in the limbs, and "heaviness with giddy or dizzy feeling in the head." She has crying spells occasionally, worrying over her condition. She was seen by Dr. O. H. Perry Pepper at my request, who reported also that her clotting and bleeding time was normal.

There is no history of hemophilia in the family and none of the family bleed excessively from cuts. One son, A. W., aged 12 years, has several small telangiectases, and a large pale reddish nevus on the back of the left shoulder and one telangiectatic lesion below the right lower eyelid. He does not bleed from the nose; the eldest son, L. W., aged 23 years, apparently has neither epistaxis nor many telangiectases. There are a few over the scapular regions (supraspinous), and one lesion about four inches below and to the left of the left nipple.

At the time of the "stroke," and since, the patient, Mrs. R. W., has been seen by A. E. Roussel, F. X. Dercum, Charles Potts, W. G. Spiller, A. Gordon of Philadelphia, T. D. Taggart of Atlantic City, N. J., S. S. Butler of Camden, N. J., and others, during the past three years; however, none of them made the diagnosis of hereditary telangiectasia with recurring hemorrhages, and did not associate the nosebleed and the cerebral complications with the hereditary weakness of the vascular system. Dr. O. H. P. Pepper agreed with me in my diagnosis.

Case 2.—Mrs. Anna L., aged 32 years; married seven years, had one miscarriage at six months, and one premature birth at eight months, the child living only twenty-four hours. Her husband had a positive Wassermann test. The patient had a positive Wassermann nine years ago. She has one boy, M. L., aged 7 years, living and well. The boy does not bleed from the nose. The patient has had nosebleed since early childhood, very frequent; bleeding stops of itself. Had influenza and pneumonia and measles. She bleeds very profusely from the left nostril. Her hands are cold, and she gets short of breath on exertion. Occasionally, she bleeds from hemorrhoids. She has seven or eight small spots over the back, on the shoulders, two small spots back of ears, several on the left side (anteriorly) of septum of nose and one or two on right side of septum. There are a few radiating dilated capillaries around the alae of the nose. She also has clubbed fingers; these are cyanosed and cold; the lips are cyanosed and get "blue" very often. Blood pressure: systolic, 95; diastolic, 70. No cardiac murmurs were heard at time of the examination, but the heart sounds were not of good quality; they were weak and muffled. She is a sister to the above patient of Case 1, Mrs. R W., and to Mrs. E. H. (Case 3). Numerous Wassermann tests have been negative, following specific treatment taken up to a few years ago.

Case 3.—Mrs. Eliz. H., aged 35 years, has four children. She had one miscarriage. One infant, aged 1 month, died of whooping cough. She was operated on four years ago for ruptured gastric ulcer with intestinal obstruction. She has been bleeding from the nose almost daily since childhood. She says her mother bled "terribly" from the nose for a great many years, and she thinks her death was due to these severe nasal hemorrhages. She has a pinpoint lesion above the right eyebrow, three or four spots on the right cheek over the malar bone, one pinpoint lesion on the left cheek, one inch to the left of the outer angle of the left eye; three or four lesions on right half of the lower lip; one spot on the under surface of the upper lip; one on upper gum; one spot on neck at base (right side). She gets attacks of nosebleeding even during her sleep.

Case 4.—Marvin H., aged 5 years, was always well, except for severe nasal hemorrhages. He has had nosebleed daily, and during sleep, since 2 years of age. He has one spot on left cheek, one inch below outer angle of left eye, and one on right cheek, one inch below and in front of right ear. Several dilated capillaries are noted on right side of septum of nose. He had measles. Mother says boy "bleeds in streams from the nose" daily, which stops itself, after bleeding for five or six minutes. In these cases epistaxis was the first manifestation of the disease. While the hemorrhages have been severe and prolonged, there is only a comparatively mild secondary anemia. In appearance the patients do not look very anemic at all. Sometimes washing the

face, or using a handkerchief, or other very slight trauma is sufficient to bring on an attack of epistaxis.

Blood Examination.—Oct. 11, 1920: Hemoglobin, 70 per cent.; erythrocytes, 2,900,000; leukocytes, 8,000. Differential count: Polymorphonclears, 51 per cent.; small lymphocytes, 45 per cent.; large mononuclears, 3 per cent.; eosinophils, 1 per cent. Marked poikilocytosis and anisocytosis. Blood Wassermann negative.

CASES 5 AND 6.—Aaron H., aged 11 years, and Jeanette H., aged 13 years, bleed very profusely from the nose since 2 years of age. They are the children of E. H. They have "spots."

Blood Examination.—Oct. 11, 1920. Jeanette H.: Hemoglobin, 75 per cent.; erythocytes, 3,350,000; leukocytes, 7,400. Differential count: Polymorphonuclears, 72 per cent.; small mononuclears, 25 per cent.; large mononuclears, 2 per cent.; eosinophils, 1 per cent. Some anisocytosis and poikilocytosis. Blood Wassermann negative.

Aaron H.: Hemoglobin, 80 per cent.; erythrocytes, 3,250,000; leukocytes, 11,000. Differential count: Polymorphonuclears, 61 per cent.; small mononuclears, 36 per cent.; large mononuclears, 2 per cent.; eosinophils, 1 per cent. Some poikilocytosis and anisocytosis. Blood Wassermann negative.

	Boggs	Test Tube
Marvin H.	5 min.	6 min.
Jeanette H.	6 min.	7 min.
Aaron H.	5 min.	4 min.

The hereditary type of telangiectases with epistaxis is principally of three forms: (1) pinpoint, (2) spider form, the most common, and (3) nodular.

Strictly speaking, telangiectasis is a dilatation of the terminal vessels, i. e., capillaries—but it is a term used also to describe dilated venules.

Osler speaks of a type of lesion occurring often on the cheeks, nose and ears in persons exposed to the weather, and in heavy drinkers. Often there occur arborescent, distended venules on the skin of the thorax along the line of the attachment of the diaphragm. Or the lesion may occur as small pinkish spots from 2 to 5 mm. in diameter, perfectly smooth and uniform, without visible venules, which disappear completely on pressure. They may be only pinpoint in size, and are often of a vivid pink color. They may appear suddenly and last for several years and then disappear. Then, again there are small nodular forms, raised, bright purple or crimson in color, from 1 to 5 mm. in diameter. They may be congenital. They are supposed to occur sometimes with cancer of the abdominal organs especially of the stomach, but they are common in old persons and in many different conditions. The spider form is made up of a central dot, from which radiate five or six venules, or rather toward which some vessels

converge (nevus araneus). Spider nevus is often associated with cirrhosis of the liver. The spots are from 2 to 3 cm. in diameter. They may occur following a roentgen-ray burn and in scleroderma. The mat form is from 1½ to 4 inches in extent. It is vivid pink in color. It may occur in cirrhosis of the liver. Osler has also seen it in a case of leukemia. Generalized acquired telangiectases, telangiectases essentielles en plaques of the French, occur in large numbers over the trunk and extremities as numerous stellate venules. This is a rare form. Stokes found about thirty-three cases. Multiple hereditary telangiectases with recurring hemorrhages is the form under discussion in this paper.

Osler,[2] Brocq [69] and Vidal [20] recognized the rare form of generalized telangiectases or telangiectases circumscripta universalis involving the skin of the trunk, the arms and legs.

Paul [70] reported the first family with this condition from Australia.

A woman, aged 32 years, had had epistaxis since childhood. At about adult life, angiomas appeared, and increased in size and number with advancing years. A dozen or more of bright red angiomatous lesions appeared on each side of the patient's face, varying from a pinpoint to a millet seed in size. The mucous membrane of the lips was extensively involved. The tongue showed numerous angiomas. A few lesions were present on the hard palate and on the conjunctival surfaces of the eyelids. An angioma on the nasal mucous membrane was present, from which hemorrhage frequently took place. This was destroyed by radium, with the result that the epistaxis was greatly diminished. There were also a few telangiectases on the palmar surface of the left hand and on the dorsal surfaces of the fingers.

In spite of the long-continued and persistent attacks of epistaxis, the patient was not anemic. Blood count: Erythrocytes, 5,110,000; leukocytes, 12,200. There was no tendency to hemophilia.

Twenty-one members of this patient's family suffered from the disease, from the greatgrandmother down to the two children of the patient, a boy, aged 3 years, and a girl, aged 7 years. The patient's greatgrandmother, grandmother, grandmother's sister, mother and mother's three brothers and one sister, the patient's six brothers and one sister, and her two children were all affected. These two children had recurring attacks of epistaxis, but no angiomas.

As to the hereditary form with hemorrhages, it is described by Osler, Weber, Hanes and Steiner. In this group of cases the lesions of dilated capillaries are confined largely to the skin of the face and the mucous membranes of the mouth and nose. The tendency to recurring nasal hemorrhages (familial in type) is a prominent feature and there is a hereditary history of recurring hemorrhages and telangiectases in the family. Angiomas of the skin associated with acromegaly have been reported only by Head.

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69. Brocq: Ann. de dermat. et syph. **8**:41, 1897.
70. Paul, S. N.: Brit. J. Dermat. **30**:41, 1918.

The lesions in the hereditary group of cases are more apt to become prominent and increase in numbers between the ages of 35 and 50. Most of these patients suffer from symptoms of a profound secondary anemia. The most common seats of the telangiectases are the cheeks, lips, ears, nose, fingers and tongue. They first appear in the skin or mucous membranes as pinpoint spots, like pinpricks, a little beneath the surface and then they increase in size and become more prominent and darker in color. A fine vascular network may be seen under the skin in some places.

DIAGNOSIS

The diagnosis is not difficult. One must avoid the mistake of diagnosing these cases as hemophilia, hemorrhagic diathesis, purpura, scurvy, or pernicious anemia, or the "phthisical state with hemorrhages." The clotting and bleeding time is always normal, and there is no history of hemophilia in these cases. The blood platelets are not appreciably reduced, and the erythrocyte resistance remains at the normal level.

TREATMENT

Treatment does not confer much relief from the hemorrhages and lesions. Iron, arsenic, calcium salts, thyroid extract and corpus luteum have all been tried with little effect. Osler once gave hypodermically 250 c.c. of a 1 per cent. gelatin solution. Calcium chlorid, 15 grains, three times daily in cinnamon water has been the remedy frequently used by me. As the bleeding seems to become more severe after the fourth decade, we must double our efforts, especially in women reaching the climacteric period, to try to stop the attacks of epistaxis, because of the high strung and tottering nervous system. Sometimes epinephrin, antipyrin solution, or hydrogen peroxid, may check the bleeding. Kephalin, thrombokinase, coagulen, thromboplastin, blood serum, whole blood, or even blood transfusion may be tried.

The chromic acid bead, electric needle, radium and even excision may be resorted to, for some of the telangiectatic lesions. The carbon dioxid stick has been used with some success.[71]

SUMMARY

1. A review of the literature on telangiectases of the hereditary type associated with familial epistaxis is given.

2. Thirty-one families afflicted with this disease are on record in medical literature. Several cases are on record which are not alto-

71. Bruck, F.: Med. Klin., Berl. **13**:505, 1917.

gether typical of this condition. They have been mentioned in this review, but are not included in the thirty-one cases.

3. No general treatment seems to be effective, owing to the congenital developmental defect of the vascular system inherent in these patients.

4. Local treatment may reduce the number and severity of the hemorrhages and improve the general condition of the patient.

5. Dermatologists, rhinolaryngologists and internists should examine patients who complain of these skin lesions (telangiectases) or recurring hemorrhages more thoroughly and analyze the family histories. In this way some previously undiagnosed or undiscovered cases may be brought to light.

6. A case of hereditary telangiectasia with severe recurring nasal hemorrhages is recorded and cases are mentioned of two married sisters, seven children and the patient's mother, all in the same family, suffering from the same disease, a total of eleven cases in one family.[72]

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72. The following references may also be consulted:

Adamson, H. G.: Brit. J. Dermat. **30**:85, 1918.
Anderson: Angiokeratoma, Brit. J. Dermat., 113 (April) 1898.
Cantrell, J.: Maryland M. J. **38**:383, 1897.
Chisholm, C.: Lancet **1**:797, 1916.
Dubreiulh: Ann. de dermat. et Syph 379, 1893.
Fiessinger, N., and Montaz, R.: Lyon chir. **14**:738, 1917.
Freudenthal, W.: Internat. J. Surg. **30**:34, 1917.
Fordyce: Angiokeratoma of Scrotum, J. Cut. Dis., p. 81, 1896.
Fox, H.: Arch. Dermat. & Syph. **1**:461 (April) 1920.
Fox, H.: Arch. f. Dermat. & Syph. **1**:229 (Feb.) 1920.
Glanzmann, E.: Jahrb. f. Kinderh. **88**:113, 1918.
Goldenberg: J. Cutan. Dis. **34**:384, 1916.
Gjessing, E.: Dermat. Ztschr. **23**:193, 1916.
Gray, A. M. H.: Proc. Roy. Soc. Med., Lond. **12**:60, 1918.
Hurwitz, S. H.: Am. J. M. Sc. **154**:689, 1917.
Knauer, I.: Arch. f. Ohrenh. Nasen, u. Kehlkopfk. **105**:14, 1919.
Little, E. G. G.: Proc. Roy. Soc. Med., Lond. **13**:13, 1919.
Langstroth, L.: Arch. Int. Med. **23**:56, 1919.
Levi and Delherm: Gaz. hebd. de méd., 1901, p. 13.
Longcope, W. T.: Med. Clin. of N. America **3**:279, 1919.
Nissim, M.: Policlinico, Rome **24**:712, 1917.
Ormsby, O. S.: Arch. Dermat. & Syph., n.s.i., 603 (May) 1920.
Osler-McCrae: Textbook Practice of Med., Ed. 9, 1920, p. 604.
Osler, W.: Riforma méd. **27**:57, 1911.
Ottenberg, R.: Med. Clin. **2**:289, 1918.
Pringle, J. J.: Proc. Roy. Soc. Med., Lond. **12**:60, 1918.
Rothmann, M.: Telangiectasis, München. med. Wchnschr. **63**:731, 1916.
Rev. de méd. **30**:22, 1911.
Rieviere, C.: Lancet **1**:697, 1916.
Sutton: Clinical Study of Angiokeratoma, J. A. M. A. **57**:189 (July 18) 1911.
Semaine méd. **28**:5, 1908.
Voss: Tidsskr. f. prakt. Med., Kristiania **8**:101, 1888.
Weber, F. P.: Brit. J. Dermat. **30**:89, 1918.

SOME FUNDAMENTAL PRINCIPLES OF ELECTROCARDIOGRAPHY *

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There are certain fundamental physical and physiologic principles concerned in the production of the human electrocardiogram, which, if thoroughly appreciated, are sufficient for an analysis of the various normal and pathologic forms of this curve. This paper will concern itself with a brief statement of these principles, their proof and their application in electrocardiography.

1. Lead II = Lead I plus Lead III. This is a law whose proof is found in the law of the conservation of energy. If this principle were not as stated, the law of the conservation of energy would be false and perpetual motion possible.

Leads I, II and III are the expressions of potential differences existing in the heart at any given moment. As these three leads lie in the frontal plane, they represent the frontal plane value of the heart's potential differences; that is, the value of cardiac potential differences situated in any planes of space as projected on the frontal plane.

If we accept Einthoven's schema of the equilateral triangle,[1] and it has been shown that it represents the conditions in the human body with sufficient accuracy,[2] then it is possible from any two leads to find the actual direction of the heart's electric tension as projected upon the frontal plane, the "angle α," and to find a value of potential difference which has a definite relation to the actual potential difference in each heart,[2] the "manifest value."

2. When the whole of the heart is in the same state of excitation, then there is no potential difference in the heart and neither Leads I, II or III, will show a galvanometer deflection, no matter what the shape of the heart or its position in the body.

Let us think of a muscle cylinder located in a cylindrical trough filled with physiologic sodium chlorid solution. Electrodes are attached at the ends of the cylinder and the electrodes connected with a galvanometer. If both ends of the muscle are excited over equal volumes of muscle substance, the two volumes of negativity cause equal and opposite potential differences in the muscle and thus counteract one another. The galvanometer will indicate no electrical activity in the muscle. If we now assume that the whole of the muscle is in the same state of excitation, then we can divide the muscle into small vol-

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* From the Department of Clinical Medicine, University of Wisconsin.

1. Einthoven, Fahr & de Waart: Pflügers Arch. **150**:275, 1913.
2. Fahr: Arch. Int. Med. **25**:146 (Jan.) 1920.

umes of substance in such a way that a volume on one side of the center of gravity corresponds in size and position to a volume on the other side. The electronegativity in the one counteracts that in the other, and the galvanometer shows no deflection.

We can think of the heart as being divided into a large number of muscle cylinders parallel to any lead we choose, and as none of these muscle cylinders will produce a potential difference for the given lead when the whole cylinder is in the same state of negativity, we can conclude that when the whole heart is in the same state of electronegativity there will be no indication of potential difference in this lead. In the same way we prove it for all leads, and thus come to the conclusion that when the whole heart is in the same state of excitation, there can be no sign of electrical activity in either Leads I, II or III.

Furthermore, it is now easy to see that the center of gravity of the muscle mass is an important point in the heart for the electrocardiographer. Every point in the muscle substance when excited causes a potential difference of such direction in the heart as would be represented by a line drawn through this point and the center of gravity. This point is negative; the center of gravity is positive. Furthermore, the farther a point is from the center of gravity, the greater the magnitude of the potential difference produced by the excitation of a given volume of muscle substance.

Looking at a frontal section of a human heart as it lies in the chest, it is seen that the greater mass of the subendocardial layers of the conducting tissue lie basally to what must be about the center of gravity of the muscle mass. When, therefore, the excitation process has spread from the main branches of the bundle into the whole of the subendocardial layers of the heart, the vector of potential must have such a direction that the base is negative to the apex. The R peak indicates excess of basal negativity in the human heart, and probably marks the end of the subendocardial spread of excitation fairly accurately.

3. The Q R S group must represent the spread of excitation throughout the ventricles, the T wave must represent the dying out of the excitation. Some have believed that the Q R S group represents the excitation of the muscle, and the T wave the contraction of the muscle. That this view is not in accordance with the facts is shown by the fact that records of the beginning of the intraventricular pressure [3] as well as heart sounds [4] show that they are already established before the Q R S group has ended, and often many 0.01 second before the beginning of the T wave. Moreover, the diphasic action current from

3. Garten: Ztschr. f. Biol. **66**:23, 1915.

4. Battaerd: Verdere graphische onderzoekingen over de acustische verschynselen van net hart. Leyden, Edward Ydo, 1913.

extrasystoles is against this view of the T representing the contraction of the muscle, the Q R S representing the excitation of the muscle.

Others have looked on the Q R S group as related to excitation and contraction and the T wave as related to metabolic processes. Against this view it may be stated that it is possible to reduce contraction to a minimum thus reducing metabolism and at the same time the Q R S, and T retain approximately their normal form and size.[5] I have in my possession records of electrocardiogram complexes Q R S and T which were not followed by a pulse at the carotid and not associated with a second heart sound. The T wave in these complexes is as large as the T wave in a preceding or following complex which was accompanied by a pulse in the carotid and a second heart sound. In the first case, the energy developed by the heart is much greater than in the second, and correspondingly the metabolism in the ordinary sense is greater, yet there is no corresponding difference in the T wave.[6] Moreover, it must be urged that in all experimental work on muscle it has been shown that the electronegative wave precedes the contraction wave by only a very short period and dies out, as a rule, only very shortly before the end of the contraction. As the heart contraction begins at about the R peak and ends just after the T wave, it is much more in accordance with the facts of muscle physiology to look on the Q R S as the representative of the spread of excitation throughout the heart muscle and the T wave as the dying out of it in the muscle. We know that the rise of negativity at a point in a muscle is very much more rapid than its decline.

4. Measurements of the direction of potential in the heart in so-called "left ventricular preponderance" show that it is actually a preponderance of right sided negativity that determines the peculiar form of the curve, and measurements of the direction of potential in "right ventricular preponderance" show that the forms of these curves are really determined by left sided preponderance of negativity in the heart.[2] It is the length of the path of conduction and the position of the center of gravity of the heart which determines so-called "left ventricular preponderance." It is not the greater negativity of a larger left or right ventricular musculature, as, I believe, Lewis[7] understands it.

I have made some necropsy measurements which support my views. In one case of combined mitral stenosis, mitral regurgitation and relative tricuspid insufficiency the electrocardiogram showed the typical

5. Noyons: Onderzoekingen gedaan in het Physiol. Lab. Utrecht, V Reeks., **11**:208, 1909. Einthoven & Rademaker: Pflugers Arch. **166**:109, 1916.

6. Einthoven & Kortweg: On the Variability of the Size of the Pulse in Cases of Auricular Fibrillation, Heart, **6**:107, 1916.

7. Lewis: Heart, **5**:367, 1914.

downward pointing Q R S group in Lead I and the high upward pointing Q R S group in Lead III. Analysis showed that the vector of potential in the heart pointed to negativity of *the left side* throughout the period of the ventricular electrocardiogram. The musculature of the left ventricle was 50 per cent. thicker than that of the right ventricle but the path of conduction along the right branch of the bundle to a point close to where the bundle breaks up into finer branches was about 1.5-2 cm. longer than the path of conduction along the left branch to the points where it begins to break up into finer branches and become lost for macroscopic vision. Measuring from these points to various points near the bases of the ventricles showed a path in the right ventricle on the average about from 3 to 4 cm. longer than in the left ventricle. Of course, such measurements are very inaccurate. They can only show in a general way that the path of conduction is longer on the one side than on the other. In the same way a necropsy of the heart of a patient who had been supporting a systolic blood pressure of over 200 for years showed a longer path of conduction in the left ventricle than in the right. The electrocardiogram was the typical electrocardiogram of so-called "left ventricular preponderance," and analysis by means of the schema of the equilateral triangle showed that negativity of the right side of the heart determined the form of this typical electrocardiogram of so-called "left ventricular preponderance."

I wish to point out that there is nearly always left ventricular preponderance of musculature even in pure mitral stenosis.[7] Therefore, if the muscle mass was the factor that determined the peculiar form of the electrocardiogram in so-called "right ventricular preponderance" we could only have "left ventricular preponderance" types of electrocardiograms.

5. The analysis of the electrocardiograms of so-called left bundle branch block indicates that the negativity gets into the left side of the heart first, and analysis of the electrocardiograms of so-called right bundle branch block indicates that the negativity gets into the right side of the heart first.[8] In other words, we have frequently been diagnosing bundle branch block on the right side when it really was on the left side, and vice versa. Recently Oppenheimer and Pardee [8] have sectioned the bundle and its branches in cases showing the bundle branch type of electrocardiogram and have confirmed my views on this subject.

6. The electrocardiogram is the expression of the action current. Its form and size depends almost entirely on the way in which the

8. Oppenheimer & Pardee: American Society for Clinical Investigaiton. Atlantic City, May 3, 1920.

excitation process spreads in the heart. There is no relation between the form and size of the electrocardiogram and the work done by the heart or the reserve power of the heart. When the whole of the heart muscle is excited and in contraction, there may be no electrocardiographic sign of activity as stated in 2. Extrasystoles which are insufficient to throw out blood into the aorta may show the highest curves, or may be exactly like normal ventricular electrocardiograms which are followed by strong ventricular contractions. Powerful hearts may show very tiny Q R S groups and small T waves, or they may show large Q R S groups and large T waves. For the sake of the clinician who has not made a thorough study of electrocardiography, it should be stated that the electrocardiogram can only answer questions as to the origin and propagation of the excitation process in the heart and can give no direct answer to the question of the contractile efficiency of the heart muscle.[9]

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9. While this paper was in the hands of the editors, a paper on "Bundle Branch Block," by Wilson and Herrmann, appeared in *Arch. Int. Med.*, August, 1920, p. 153. It is too late for me to prepare a long article on bundle branch block, but it is necessary that I come out definitely in opposition to such statements of Wilson and Herrmann, as "To assume that preponderant muscle activity at the apex of the heart must cause a downward deflection in Lead II, or that corresponding activity at the base must cause an upward deflection in the same lead as has so frequently been done; to assume, as Fahr has done, that when the electrical axis as determined by Einthoven's formula points to the left the preponderant muscle activity is on the right side of the heart is totally unjustifiable." This conclusion of Wilson and Herrmann is based on their interpretation of the distribution of potential in the cylinder B, Figure 2, of their paper when the point L is in excitation.

Their interpretation is false, in my opinion. When the point L is in excitation all other points of the muscle mass AMB are positive. There is a potential difference between A and L as well as B and L and M and L. Moreover, muscle experiments show that M is negative to A and B when the point L is in excitation and lies in the same muscle fiber or syncitium of fibers as M. The resultant of all these potential differences must be a potential difference of such a direction that the portion LM of the muscle is negative to the portions A and B. In other words, the potential difference in the cylinder must be such that the electrode S is negative to R. All this follows from the fact that all points on a muscle are positive with respect to the excited points and not just to one point as M. It makes absolutely no difference whether the point L is located in a syncitium of muscle spread over one surface of another syncitium of muscle, or whether the point L is located in one large syncitium. As a matter of fact, I do not believe that the negativity produced in the Purkinje system itself is large enough to affect the galvanometers. Experiments which I have carried out show that potential differences of the order of tenths of volts are concerned in the production of the electrocardiogram. A small flat piece of tissue like the subendocardial Purkinje system would not, in all probability, produce voltages this high.

Furthermore, I wish to point out to Wilson and Herrmann that most of Lewis' dog experiments agree with my interpretation of bundle branch block, and that Oppenheimer's examinations of hearts of bundle branch block certainly do not support the accepted view of bundle branch lesions.

ACHOLURIC JAUNDICE *

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Acholuric jaundice has long been recognized and frequently seen in many conditions with various clinical designations. Most commonly it is ascribed to some disorder of the liver or to anemia, but because no bile appears in the urine little investigation has been made of such jaundice. In 1917 [1] I reported an investigation of the blood in pernicious anemia and found that fifteen out of twenty patients had bilirubin in the plasma and none had it in the urine. I concluded from these findings that bile pigment was in some way fixed to the blood plasma and could not be excreted by the kidney. Previously Dr. Hoover and I reported [2] a series of observations under the title of "Dissociated Jaundice," in which it was pointed out that biliary elements occur in the blood in varying amounts; that there is a fairly constant "threshold" for these substances above which they appear in the urine; but that in some conditions, principally diseases of the liver and the anemias, this threshold is quite high. In many subsequent observations, this same thing has been observed, and I have also found both dialyzable and nondialyzable bile pigment in the blood—nondialyzable alone in the milder grades of jaundice, and both dialyzable and nondialyzable in the more severe grades of jaundice. I also reported that, when dialyzable pigment was present in the blood, bile pigment was usually found in the urine; and when no pigment could be dialyzed from the blood, none would be found in the urine. There have been very few exceptions to the rule that bile pigment of the blood diffuses through collodion membrane whenever it goes through the kidney.

This method of study has disclosed many cases of acholuric jaundice, some so faintly jaundiced that a chemical test of the plasma with nitric acid was the only evidence of jaundice, others so very yellow that the absence of choluria demanded explanation. In a very few of the latter cases, impairment of kidney function could be admitted as a possible cause. In others, where no defect in kidney function could be found, it was assumed that something peculiar to the conditions of cholemia determined the retention of pigment. This report,

* Read before the Association of American Physicians, May, 1920.

1. Blankenhorn, M. A.: The Bile Content of the Blood in Pernicious Anemia, Arch. Int. Med., **19**:344 (March) 1917.

2. Hoover, C. F., and Blankenhorn, M. A.: Dissociated Jaundice, Arch. Int. Med., **18**:289 (Aug.) 1916.

then, deals with the nature of such bile pigment as could not be dialyzed from the blood plasma and did not appear in the urine.

The specimens dealt with in every case were oxalate plasma free from hemolysis, obtained from patients that were admitted to the medical wards for study and treatment. In every instance the urine was examined for bile and an inspection was made of the skin and sclerae for jaundice. Also, jaundiced specimens of plasma were fabricated in the laboratory by adding various amounts of fresh gallbladder bile to freshly obtained oxalate plasma. It was found that, when sufficient gallbladder bile was added to give the plasma a deep yellow stain, the plasma, when dialyzed in water, would give only a part of the bile pigment, and that prolonged dialysis in running water would not completely decolorize the plasma to its original condition. The amount of pigment thus remaining undialyzable is quite variable. When plasma was stained for a short time by weak solutions of bile, less remained as undialyzable; when stained for longer periods and with stronger solutions, considerably more remained. It was also found that when colorless plasma was placed within the collodion sac, with a dilute aqueous solution of gallbladder bile surrounding the sac, the bile pigment would penetrate the membrane and stain the plasma, but subsequently could not be removed completely by dialysis.

Jaundiced plasma obtained from forty patients was dialyzed into small amounts of water to determine the presence of any dialyzable pigment, and if any was found the plasma was then dialyzed for twenty-four hours in running water, the nondialyzable residue being preserved. In no instance was it possible completely to decolorize plasma by dialysis. But there was quite a wide variation in the amount of undialyzable residue in different specimens.

It was found that when the proteins were removed from plasma by coagulation with heat, the coagulated proteins were stained yellow or yellowish green, and that when only nondialyzable pigment was present, coagulation of the plasma and filtration removed all of the color. In plasma that contained dialyzable as well as nondialyzable pigment, coagulation by heat and filtration did not remove all color. However, after such specimens were dialyzed with running water for twenty-four hours, thus removing all dialyzable pigment, and then coagulated with heat, filtrating would remove all of the color. It was then apparent that nondialyzable bile pigment is associated with the protein of the plasma. When the proteins of the plasma were removed by salting out and were then precipitated, the precipitate was found to be yellow or green, depending on the amount of pigment present.

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3. Marowitz, P.: Handb. d. Biochem. des. Mensch. u. d. Thiere, **2**:pt. 2, p. 79.

After complete precipitation by salting out, the filtrate would be entirely colorless and give no biuret reaction. When proteins were salted out fractionally [3] by ammonium sulphate, all three elements—euglobulin, pseudoglobulin, and serum albumin—were found to be pigmented.

Heat coagulated proteins could be washed with water, dilute acids and alkalies without losing any of their pigment. When extracted with alcohol, the pigment was removed quickly and entirely, and could then be identified as bile pigment by the various color tests. No pigment could be removed by prolonged extraction with ether or petroleum ether from ten specimens thus treated. Strong acids or alkalies did dissolve the coagulated proteins and decolorize their added pigment, but they did not extract the pigment unchanged as does alcohol.

Precipitated proteins which are stained by bile pigments behaved in the same manner to solvents, i. e., they gave up their bile pigments only to alcohol, and not to dilute acids and alkalies or to ether and petroleum ether.

When heat coagulated proteins or precipitated proteins were acted on by pepsin, they went into solution readily and still retained their yellow or green color. When dialyzed in this form, a certain amount of bile pigment would dialyze but not until some of the protein, probably peptone, was dialyzed; that is, the undigested protein, together with its pigment, does not dialyze at all, but when acted on by proteolytic enzymes, metaproteins are formed which are more diffusible but which apparently retain their stain of bile pigment. In no instance was any staining substance found in the plasma which could not be coagulated out by heat and precipitated by salting out. It would appear, therfore, that nondialyzable bile pigment in the blood is combined with the proteins by adsorption, like a colloid stained by a dye.

In a previous report, I offered the suggestion that acholuric jaundice might be explained by retention of bile pigments in the blood, but that such pigment was essentially different from that which was readily dialyzed. I was led to believe this by noticing that in obstructive jaundice, which is the simplest type of jaundice, there is very little nondialyzable pigment in the blood; but in diseases of the liver, particularly of long standing, there is usually a large amount of nondialyzable pigment. This suggested that the formation of nonobstructive jaundice was not simply a process of pouring bile pigment into the blood stream, and that the pigment by its elaboration in the liver was of a different nature from pigment found in obstructive jaundice. However, on further study of the various types of acholuric jaundice, this appearance of a different pigment was not substantiated. It was noted, however, that most of the cases of acholuric jaundice have been jaundiced for a long time. When severely jaun-

diced for a long time, there is a large amount of nondialyzable bile pigment; when mildly jaundiced for a long time, there is a less degree. It is quite probable that the retention of bile pigment can be explained as a staining of the blood proteins, and that the degree of stain varies according to the concentration of the stain and the length of time that the plasma is exposed to the stain.

CORRESPONDENCE

THE EFFECT OF CERTAIN BLOOD CONSTITUENTS ON PICRATE SOLUTIONS

To the Editor:—In a recent number of the ARCHIVES OF INTERNAL MEDICINE Cowie and Parsons[1] report the effect of certain blood constituents on picrate solutions. As a result of their studies, they conclude that creatinin, acetone, diacetic acid and epinephrin react with the picrate solution employed in the modified Lewis-Benedict method for blood sugar determination; and, further, that the reaction given by acetone and by epinephrin, is so intense that these substances become possible serious interfering substances in the determination of blood sugar by the modified Lewis-Benedict method.

The possible interference by creatinin in the determination of sugar in blood by the picrate method has been the subject of frequent comment in the literature, and it is not our purpose to enter into any discussion of this question at the present time. It may, however, be pointed out that in certain bloods (particularly those of advanced nephritis or uremia) creatinin may contribute something toward the blood sugar figures. Except in rare cases, however, this interference can amount to only a few milligrams of sugar per hundred c.c. of blood.

The figures reported by Cowie and Parsons for interference by acetone and by epinephrin are so astonishing, and so contrary to our experience, that we feel they require some comment in justice to the large numbers of workers who have employed the picrate method of sugar determination in the blood.

Cowie and Parsons state that when added in moderate amounts to pure picrate solutions acetone has very little effect on the developmentt of color; that the acetone "blows off" under such conditions. When, however, acetone is added to blood, these investigators find that they can detect a distinct color change in the picrate solution when adding 2 c.c. of a solution containing 0.05 mg. of acetone per hundred c.c. of solution to 2 c.c. of blood. Since only very moderate success was had in detecting glucose added to blood (25 mg. of glucose per hundred c.c. of solution was the smallest quantity they could detect), Cowie and Parsons conclude that the picrate solution is five hundred times as sensitive to acetone as to glucose. Only a moment's reflection is required to show that any such conclusion as this cannot be correct by quite a large margin. Normal blood may contain as much as 1 mg. of acetone per hundred c.c. of blood. If the picrate solution is five hundred times as sensitive to acetone as to sugar, such bloods would show 0.5 per cent. of glucose due to the acetone alone, and in cases of diabetes, where the acetone content of the blood may be very considerably increased, figures of from 5 to 10 per cent. of sugar in the blood would be quite common.

Our own experiments with acetone have shown that the substance affects the picrate solution approximately to the same degree whether the acetone be added to water or to blood. This finding is what we should expect. When added to blood, acetone is not detectable in the picrate method for blood sugar determination until the quantity added exceeds 7 mg. per hundred c.c. of blood. With larger quantities of acetone the effect becomes more marked with each addition so that when 20 or more mg. of acetone per hundred c.c. are added, the acetone has somewhat more effect than an equal weight of glucose.

It is plain from these findings that acetone cannot be regarded as constituting a really serious interfering substance in the determination of blood sugar by the picrate method. In any case, acetone can be removed quantitatively from blood filtrates by boiling for about half a minute. The filtrate should then be cooled before addition of the carbonate, and the determination

1. Cowie, D. M., and Parsons, J. P.: Studies on Blood Sugar: Effect of Blood Constituents on Picrate Solutions, Arch. Int. Med. **26**:333 (Sept.) 1920.

carried out as usual. It will be very rare, indeed, that this boiling of the filtrate will have any effect whatever on the blood sugar found, since acetone seldom occurs in appreciable amounts in blood. Only in cases where the urine is rich in acetone bodies would it be worth while to employ the preliminary boiling.

In Table 11 of their paper, Cowie and Parsons report that they can detect an effect of epinephrin when using 2 c.c. of a solution containing 1 mg. of this substance in 4,000,000 c.c. of water. This would mean that the picrate solution would detect 1 part of epinephrin in 4,000,000,000 parts of solution, indicating entrance into a realm of analytical chemistry into which no one hitherto has entered.

We have carried out experiments with epinephrin, making use of fresh solutions prepared from the free base (adrenalin; Parke, Davis & Co.) with the help of a little hydrochloric acid. We also used the Parke, Davis solution of adrenalin chlorid (1:1,000, which contains about five times as much chloretone as adrenalin). The results of our work in this connection are wholly at variance with those reported by Cowie and Parsons. We find that epinephrin has little more effect than twice its weight of glucose on the picrate solution, either in pure solution or when added to blood. Since epinephrin cannot be demonstrated in systemic blood, or is certainly not present in a concentration greater than 1 part in several million, its possible interference in the picrate method for blood sugar is not worthy of consideration.

We can offer no explanation of the discrepancy between our results with acetone and epinephrin and those reported by Cowie and Parsons. We believe, however, that such results as have been reported by Cowie and Parsons in this connection cannot be duplicated in any properly conducted experiments.

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New York.

STUDIES ON BLOOD SUGAR: EFFECT OF BLOOD CONSTITUENTS ON PICRATE SOLUTIONS

To the Editor:—Our paper on Studies on Blood Sugar: The Effect of Blood Constituents on Picrate Solutions, published in the ARCHIVES OF INTERNAL MEDICINE, September, 1920, p. 333, contained a typographical error, p. 338, Table 11. Heading of first column should read "Size of blood sample," not "water sample."

We should also like to make the following additions:

Reference 4, page 338, after the words "(per liter)" should follow, Van Slyke and Fitz: J. Biol. Chem. **32**:497, 1917.

After the words, "the acetone blows off," page 338, should follow an asterisk with this footnote: "Samples run with 100, 75, 50, 25, 15 mg. to 100 c.c. of water were practically black; no attempt was made to read them." This sentence should be omitted from the asterisk reference on page 339.

A question has been asked as to why we got the readings 0.040 in our blank determinations. This is the point on the vernier at which the solutions became unreadable. When we got to this point the prism was just emerging from the solution. We could not call it 0.000 and we do not believe it is 0.000. We have had blanks read in different departments of the hospital and by different men who always bring in the figures from 0.032 to 0.040. The same thing happens with the creatinin test of Folin where a picrate solution is used. Readings of blanks handed out to technicians as unknowns always come back 0.040 to 0.048. These points are practically unreadable.

We used a Dubosque colorimeter for all our work.

DAVID MURRAY COWIE, M.D.,
JOHN PURL PARSONS, M.D.,
Ann Arbor, Mich.

BOOK REVIEWS

PATHOGENIC MICRO-ORGANISMS. A Practical Manual for Students, Physicians and Health Officers. PARK & WILLIAMS. Assisted by CHARLES KRUMWIEDE, JR. Lea & Febiger, New York, 1920.

This well known textbook appears in its seventh edition. It is now a book of nearly 800 pages, clearly printed on good paper and containing nine full page plates and 214 engraved illustrations, most of which are well selected and well done. It is divided into three parts, Part I dealing with the general characteristics and methods of study of all pathogens; Part II with the detailed studies of individual organisms, and Part III with applied microbiology.

Part III is, in a way, the most distinctive feature of the book. In it are discussed such subjects as bacteriology of milk, water, air, soil, shell fish, etc.; also the application of vaccines and serums, where, under separate headings, these topics for the various infections are treated, as a rule, briefly. This mode of treatment necessitates the separation of subjects, natural units in themselves, and, to some degree at least, is disadvantageous. But it has its redeeming feature in that the discussion of the field of vaccine and serum therapy becomes easily accessible and the various infections may be correlated in respect to treatment.

New data has been inserted in most of the chapters and some chapters have been rewritten entirely. In respect to mass of data presented, this book surpasses most, if not all, other texts. It is well arranged and coordinated.

As one glances through the pages one is struck by the abundant use that has been made of data that has accumulated largely through studies carried on at the Department of Health of New York City. In a way, this is a desirable feature, since it enables the authors to present much first hand information. This statement does not imply that other sources of information have been neglected. On the whole, a fairly abundant bibliography is presented in the text. The authors have made abundant use of information derived from studies carried on during the war. Such subjects as war wounds, anaerobic bacteria and vaccination are discussed in the light of this experience. And the difficult subject of the bacteriology of influenza is presented in a sane and sensible way. It is gratifying to pathologists and bacteriologists to note the increasing number of satisfactory American texts, of which this is one, on the subject of pathogenic bacteria. In marked contrast one cannot refrain from pointing out the general inadequacy of our American texts in the closely related subject of general pathology.

EPIDEMIC ENCEPHALITIS (ENCEPHALITIS LETHARGICA). By FREDERICK TILNEY, M.D., PH.D., Professor of Neurology, Columbia University; Attending Neurologist, the Presbyterian Hospital, and the New York Neurological Institute; Consulting Neurologist, Roosevelt Hospital, New York, and HUBERT S. HOWE, A.M., M.D., Instructor in Neurology, Columbia University, Assistant Visiting Neurologist, the Presbyterian Hospital, New York. Pp. 252. New York: Paul B. Hoeber, 1920.

This book is an expansion of articles by Tilney and Riley (*Neurological Bulletin*, March, 1919) and Howe (*Neurological Bulletin*, May, 1919), with additions and further elaboration of original clinical and pathological material. There is also a general discussion of the various aspects of the disease, based on the authors' cases and reports in the literature. The book contains valuable and original detailed data, but does not give a comprehensive review of the literature of the disease, and the material—while rich and described with dependable accuracy—is not as fully elaborated as may be desired by busy readers. There are fifty-three illustrations, many of which are taken from the previously mentioned articles by the same authors.

PASTEUR: THE HISTORY OF A MIND. By Emile Duclaux. Translated and edited by Erwin F. Smith and Florence Hedges. Octavo. Cloth. Pp. 363. Illustrated. Philadelphia and London: W. B. Saunders Co., 1920.

It was an excellent idea of the senior translator to publish this work at this particular time, although the bitter words of Declaux in a letter written in 1882 still have some application. He said: "I know very well that old physicians do not read any more, and when they do read they do not understand. I know that students think only of their examinations, when they think at all." For some years everything except the daily task had to be neglected. Now we should go back to the cultivation not only of technical matters, but of all that gives a wider knowledge of the growth of medical and biologic sciences and of the great men who have had a part in advancing them. Everyone knows that Pasteur was one of the greatest factors in the vast progress of the last fifty years, but what he did and how he did it will always be profitable to recall. His life and his works have been available for some years in the intimate and sympathetic pages of René Vallery-Radot. Professor Duclaux, who had worked from an early day as pupil and as colleague of Pasteur, and whose generous appreciation of the master was based on the most thorough familiarity with his researches, wrote almost wholly with an eye to the technical and scientific aspects of Pasteur's work, so the two books supplement each other. But, the present work has a great advantage over the original French edition. Dr. Smith has put in the form of an introduction of two dozen pages not only a warm eulogy of Duclaux, but also so beautiful a picture of his life and work that the book might well be called the history of two minds, still better, to use the French word which does not seem adequately rendered by "mind," two "esprits." There is also a very useful "Annotated List of Persons Mentioned in This Book," and reproductions of many portraits of Pasteur and of Duclaux. The index is much superior to those usually found in works of this kind. The translation is, as a rule, smooth and accurate, so much so that one notes with surprise the use of "marine salt" for common salt or sodium chlorid. Public libraries, as well as medical libraries, should place the book where it can be seen and read by all classes of readers, for although Pasteur's period is rapidly receding, his influence on biology in general and on bacteriology in particular was far reaching. Unfortunately, the high price of the volume, though not out of proportion to the cost of getting it up, will prevent many who would wish to own it from having that pleasure.